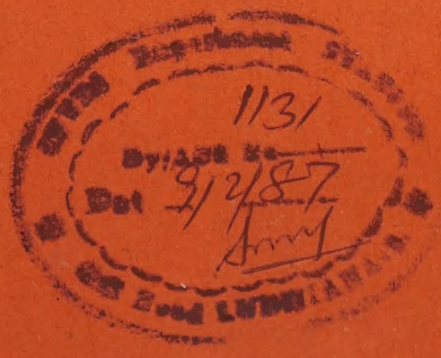
Indian J. Chem. Vol. 25B No. 12, pp. 1191-1280
DECEMBER 1986
CODEN : IJOCAP ISSN : 0019-5103
25B(12) 1191-1280 (1986)

INDIAN JOURNAL OF CHEMISTRY

SECTION B
(Organic including Medicinal)



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Section B: Organic Chemistry including Medicinal Chemistry

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Editor-in-Chief: S.P. Ambasta

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Indian Journal of Chemistry

Sect. B: Organic Chemistry, including Medicinal Chemistry

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Indian Journal of Chemistry
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Stereoselectivity & Stereospecificity in Reductions of Some Hexahydro-3-oxophenanthrene Derivatives with Various Reducing Agents[a]

S K CHATTERJEE, S BHATTACHARYA, S R RAYCHAUDHURI & A CHATTERJEE*
Department of Chemistry, Jadavpur University, Calcutta 700 032

Received 28 *April* 1986; *accepted* 8 *July* 1986

Catalytic and chemical reduction of hexahydro-3-oxophenanthrene derivatives (**1a, b**) and (**1d, e**) are reported. Catalytic hydrogenation (Pd/C, 10%) of **1a** and **1b** in acidic medium affords predominantly the *trans*-fused hydrocarbons (**2a**) and (**2c**) respectively, whereas similar hydrogenation of **1a** in pyridine solution gives the *cis*-fused ketone (**3b**) as the major product. Birch reduction of **1a** and **1b** affords in each case a 65 : 35 mixture of the corresponding saturated *cis*- and *trans*-fused ketones. Reduction of **1a** and **1b** with Ni-Al alloy and alkali followed by oxidation furnish selectively the *trans*-fused ketones (**3a**) and (**3c**). Lithium aluminium hydride reduction of **1a, b** and **1d, e** followed by oxidation provided exclusively the *cis*-fused ketones (**3b**), (**3d**), (**3f**), and (**3h**) respectively. The stereospecificity observed in LAH reduction, and the lower yields of the reduction products in the case of **1b** and **1e**, have been rationalised.

In connection with some other problems, we searched for a method for the exclusive *cis*-reduction of the hexahydro-3-oxophenanthrene derivative (**1a**). We report herein our results on the stereochemical outcome of the reduction of **1a** and related compounds (**1b**) and (**1d, e**) with various reducing agents leading to a general and efficient procedure for the predominant *trans* and stereospecific *cis*-reduction of the above unsaturated compounds. It is interesting to note that of all the reducing agents employed, LAH in refluxing THF gave exclusively, in each case, the product with *cis*-stereochemistry at the ring-fusion.

Catalytic and chemical reduction of **1a, b** *and* **1d, e**: *Catalytic reduction*

The unknown unsaturated ketone (**1a**) was easily prepared through the usual Robinson annelation of 2,7-dimethyl-1-tetralone[1]. Catalytic reduction of **1a** was studied under different conditions, and the products were characterised through GLC and PMR spectra. Hydrogenation of **1a** over 10% Pd/C in acetic acid containing perchloric acid led directly to a 90:10 mixture of the *trans*-**2a** and *cis*-**2b** hydrocarbons in 78% yield. The more polar products, isolated through chromatography, were shown by GLC to be approximately 1:2 mixture of *cis*-**3b** and *trans*-**3a** ketones and 1:5 mixture of *cis*-**4b** and *trans*-**4a** alcohols respectively. The stereoselective formation of *trans*-hydrocarbon (**2a**) probably proceeds through the intermediate allylic alcohol formed from **1a**. This contention is supported by the fact that the crude allyl alcohol, prepared from **1a**, on catalytic hydrogenation under similar condition, furnished a 86:14 mixture of *trans*-**2a** and *cis*-**2b** hydrocarbons. Similar reduction of unsaturated methoxyketone (**1b**)[2] afforded in moderate yield the *trans*-hydrocarbon (**2c**). It may be mentioned that the allyl alcohols, derived from the unsaturated ketones (**1b**)[2] and (**1c**)[3] on catalytic reduction over palladised strontium carbonate, are reported[2,3] to provide the corresponding saturated alcohols with *trans*-ring fusion.

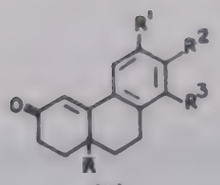
Catalytic hydrogenation (Pd-C, 10%) of **1a** under neutral condition furnished a 93:7 mixture of the saturated *trans*-**2a** and *cis*-**2b** hydrocarbons in 50% yield and a 58;42 mixture of saturated *trans*-**3a** and *cis*-**3b** ketones in 40% yield.

Catalytic reduction of several Δ^4-3-ketosteroids in pyridine as a solvent is known[4] to provide the 5β-isomer in predominant amount. Such reduction of the ketone (**1a**) in pyridine solution was rewarding as it provided a 85:15 mixture of *cis*-**3b** and *trans*-**3a** ketones in 90% yield.

Reduction with lithium metal in liquid ammonia

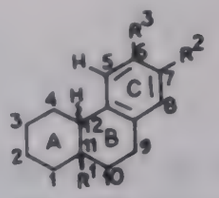
Lithium-liquid ammonia reduction of **1a** using ammonium chloride as the proton source furnished in excellent yield a 65:35 mixture of the saturated *cis*-**3b** and *trans*-**3a** ketones. The related methoxyketone (**1b**) on similar reduction afforded in good yield the same mixture (63:37) of *cis*-**3d** and *trans*-**3c** ketones indicating that the electronic effect of the methoxyl group did not influence the stereochemical course of this reduction. A small amount of a crystalline hydroxy compound was also isolated from this reduction, and the stereostructure (**4c**) assigned to this is supported from the experiments described below. It is worth mentioning here that similar Birch reduction

[a]For a preliminary report on a part of this work, see Chatterjee A, Raychaudhuri S R & Chatterjee S K, *Chem Commun*, (1982) 24.



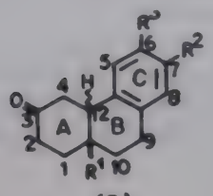
(1)

a, R = R¹ = Me, R² = R³ = H
b, R = Me, R¹ = R³ = H, R² = OMe
c, R = Me, R¹ = H, R² = OMe, R³ = Me
d, R = R¹ = R² = R³ = H
e, R = R¹ = R³ = H, R² = OMe



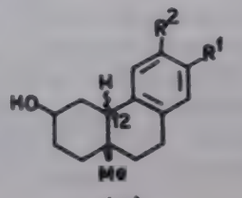
(2)

a; 12α H, R¹ = Me, R² = H, R³ = Me
b; 12β H, R¹ = Me, R² = H, R³ = Me
c; 12α H, R¹ = Me, R² = OMe, R³ = H
d; 12β H, R¹ = Me, R² = OMe, R³ = H
e; 12β H, R¹ = R² = R³ = H



(3)

a; 12α H, R¹ = R³ = Me, R² = H
b; 12β H, R¹ = R³ = Me, R² = H
c; 12α H, R¹ = Me, R² = OMe, R³ = H
d; 12β H, R¹ = Me, R² = OMe, R³ = H
e; 12α H, R¹ = R² = R³ = H
f; 12β H, R¹ = R² = R³ = H
g; 12α H, R¹ = R³ = H, R² = OMe
h; 12β H, R¹ = R³ = H, R² = OMe



(4)

a; 12α H, R¹ = H, R² = Me
b; 12β H, R¹ = H, R² = Me
c; 12α H, R¹ = OMe, R² = H

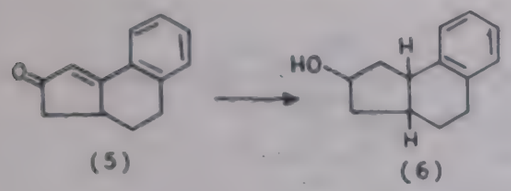
of the related methoxyketone (**1c**)[3] was reported earlier to give, as the major product, the corresponding *trans*-ketone. The direction of protonation of the much less basic benzylic carbanion intermediate in these reductions depends upon a number of factors[5], and a mixture of stereo-isomeric products are usually expected, and this what we have observed. In support of our results, it may be mentioned that the methoxyketone (**1e**), lacking the angular methyl group, on metal-ammonia reduction, furnished[6] the corresponding *cis*-ketone (**3h**) as the major product.

Reduction with nickel-aluminium alloy and alkali

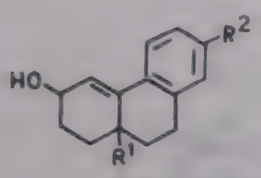
Reduction of styryl ketones with Ni-Al alloy in aqueous or ethanolic solution of sodium hydroxide is known to furnish the corresponding saturated ketones[7] or saturated alcohols[8]. Such reduction of the styryl ketones, having α,β-unsaturated carbonyl chromophore as part of a 6,5 or 5,5-fused ring system, is reported[9] to furnish in each case a single saturated alcohol with *cis*-stereochemistry at the ring junction as shown in the case of **5** which furnished the *cis*-compound (**6**). We were therefore interested to investigate in detail the stereochemical course of such reduction of our styrenoid ketones (**1a, b**) and (**1d, e**) with 6,6-fused ring system*. Reduction of **1a** with Ni-Al alloy by the prescribed procedure[9] led to a mixture of saturated alcohols which on oxidation with pyridinium chlorochromate[10] provided in near quantitative yield a 92:8 mixture (GLC) of the saturated *trans*-**3a** and *cis*-**3b** ketones. Recrystallisation of this solid mixture finally afforded the pure *trans*-**3a** in good yield. The methoxyketone (**1b**) similarly provided a mixture of saturated alcohols from which the crystalline alcohol (**4c**), mentioned earlier, could be isolated. Oxidation of the above crude alcoholic product furnished in excellent yield a crystalline material as a 89:11 mixture (GLC) of the saturated ketones *trans*-**3c** and *cis*-**3d**. This mixture finally provided the pure *trans*-**3c** in respectable yield. The *trans*-ring fusion of the alcohol (**4c**) follows mainly from its C-5 aromatic proton doublet at δ 7.10 (J = 8 Hz), and also from its oxidation to the ketone, *trans*-**3c**. As **4c** was also isolated as a byproduct in the Birch reduction of **1b**, the configuration of the hydroxyl group in **4c** is tentatively assigned as equatorial.

The unsaturated ketones (**1d**)[11] and (**1e**)[12], lacking the angular methyl group, on Ni-Al alloy reduction followed by oxidation afforded, in each case in mod-

*As far as we know, reduction of this system with Ni-Al alloy in base has not been reported earlier.



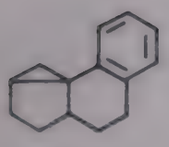
(5) (6)



(7)

a; R^1 = Me, R^2 = OMe

b; R^1 = R^2 = H



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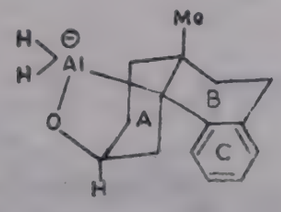

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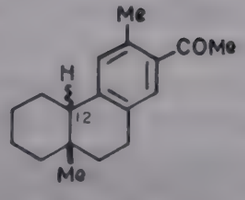


(11)

a; 12 α H

b; 12 β H

erate yield, a stereoisomeric mixture of ketones, not resolvable by GLC or by chromatography. The ketonic material, obtained from **1e**, on careful fractional crystallisation furnished the ketones, *trans*-**3g**[12] and *cis*-**3h**[12] in a ratio of around 1:1.

Ni-Al alloy reduction of the unsaturated ketones (**1a, b**) with angular methyl group seems to be highly stereoselective providing predominantly the *trans*-products. A stereoisomeric mixture of the saturated ketones (**3c, d**) on reduction with Ni-Al alloy as above afforded a mixture containing mainly the saturated alcohol (**4c**); but the allyl alcohol (**7a**), prepared from **1b**, was completely recovered unchanged under the above reduction condition. These findings indicate that the allyl alcohol is not the intermediate in this type of reduction. Radical anion or dianion is also probably not involved as Birch reduction of **1a, b**, described earlier, provided different stereochemical results.

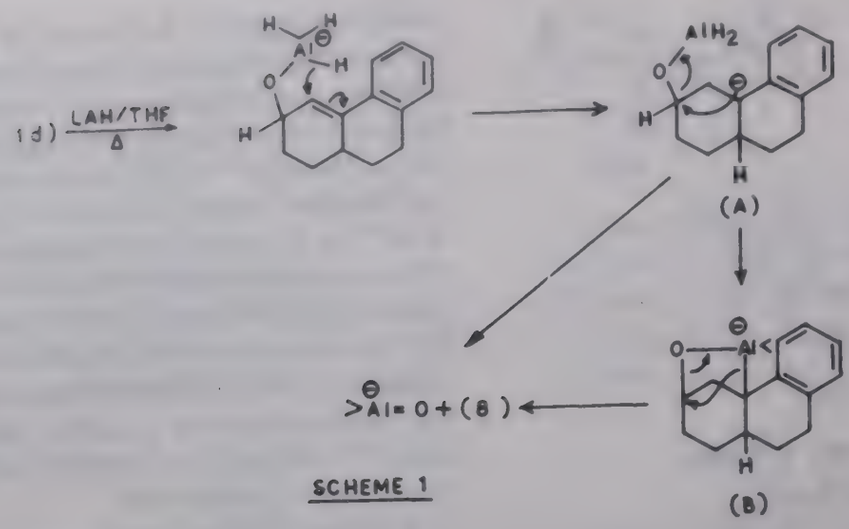
Reduction with lithium aluminium hydride (LAH)

Double bond reduction of α,β-unsaturated carbonyl and other related compounds with LAH is quite well-documented[13]. Reduction of double bonds of certain strained and rigid homoallylic alcohols[13d,e] by LAH has also been reported. The mechanism of double bond reduction was investigated mainly by Franzus and Snyder[13d] in norbornane series, by Snyder[13f] and Borden[13c] in the cinnamic series, and by Fetizon *et al.*[13g] in the case of steroidal dienones. In all the above cases, reduction of the double bond was shown to proceed stereospecifically through intramolecular five- or six-centre hydride transfer from the alkoxyaluminium hydride. The high stereospecificity of double bond reduction in some cases was rationalised[13c–f] through the formation of five-membered cyclic alane intermediate.

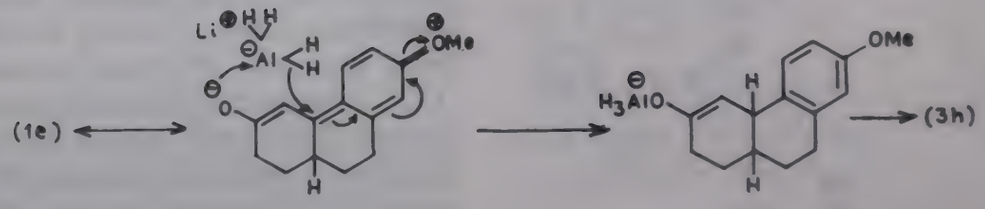
With this background information, we were tempted to investigate the LAH reduction of ketone **1a**. Reduction of **1a** with an excess of LAH in refluxing tetrahydrofuran (THF), a solvent of choice[14] for double bond reduction, furnished interestingly, a single (GLC) saturated alcohol which on oxidation with pyridinium dichromate[15] gave in an overall yield (76%) the desired saturated ketone *cis*-**3b**. Similar hydride reduction of the related ketone (**1b**)[3], carrying a *p*-methoxyl group, afforded a mixture of saturated and unsaturated alcohols. Oxidation of this mixture gave a ketonic material (IR: 1710s and 1655s cm^{-1}), chromatographic purification of which led to the crystalline *cis*-ketone (**3d**) in moderate yield (52%); not a trace of isomeric *trans*-**3c** could be detected by GLC.

Above reduction procedure was then extended to the related unsaturated ketones (**1d**)[11] and (**1e**)[12], lacking the angular methyl group. The crude reduction product from **1d** was non-ketonic and on chromatography (see Experimental) afforded a hydrocarbon (16%, homogeneous by GLC), and an alcoholic fraction. The hydrocarbon fraction was tentatively assigned as the cyclopropyl derivative (**8**), especially from its elemental analyses, mass and PMR spectra. Catalytic hydrogenolysis of **8** provided a product whose mass spectrum indicated that the cyclopropane ring has opened up as expected. The formation of **8** directly from the intermediate benzylic carbanion (**A**) or through the alane intermediate (**B**) (Scheme 1) is not unexpected[16]. The above alcoholic fraction, obtained from LAH reduction of **1d** on oxidation followed by chromatography furnished the known crystalline *cis*-ketone (**3f**)[17] in moderate yield (45%), and the unoxidised crystalline allyl alcohol (**7b**, 18%) which could be further oxidised to the starting **1d**.

The unsaturated methoxyketone (**1e**) on similar LAH reduction afforded a crude product (IR: 3600 and 1710w cm^{-1}) which on oxidation as before gave a ketonic material. Chromatographic purification led to the *cis*-ketone (**3h**)[12] in acceptable yield. The weak



SCHEME 1



SCHEME 2

IR band at 1710 cm^{-1} in the crude reduction product probably suggests the presence of a small amount of the *cis*-ketone (**3h**), and this is supported comparative GLC, and its formation may be rationalised through the pathways shown in Scheme 2.

As shown above, the unsaturated methoxyketones (**1b**) and (**1e**) on LAH reduction followed by oxidation afforded the saturated *cis*-ketones (**3d**) and (**3h**) in lower yield (~ 50%) than that (76%) realised from the unsaturated ketone (**1a**), having no *p*-OMe group. This may possibly be due to the resonance effect of the *p*-OMe group which impedes[c] conventional five-centre hydride transfer to the styrene double bond by destablishing, to a certain extent, the intermediate benzylic carbanion (**9**) as shown in Scheme 3. The moderate yield (45%) of the *cis*-ketone (**3f**) from the simpler unsaturated ketone (**1d**) may partly[d] be due to the formation of other products such as the cyclopropane compound (**8**), and the allyl alcohol (**7**) reported above.

The above procedure seems to be a general method for the stereospecific synthesis of the *cis*-ketones of octahydrophenanthrene series. Stereochemical evidence of the above hydride reduction suggests that the reaction is intramolecular and the formation of a carbon-aluminium bond[e] as shown in **10** (Al not tetrahedral) is probably necessary. In the case of the unsaturated methoxyketones (**1b**) and (**1e**), the alternative pathway[f] (Scheme 4) for the formation of the *cis*-ketones (**3d**) and (**3h**) may not be altogether ruled out. The results so far obtained indicate that the generation of the intermediate (**10**) is probably sterically assisted by the angular methyl group.

Stereochemistry of saturated ketones

Although the *cis*-ketone (**3d**) usually equilibrates between the two possible conformers, its complete structure and stereochemistry has been determined by X-ray crystal structure analysis[g]. The analysis shows clearly that in the crystalline state, the angular methyl group in the **3d** is equatorial to ring-A, and axial to ring-B having half-chair conformation. The PMR

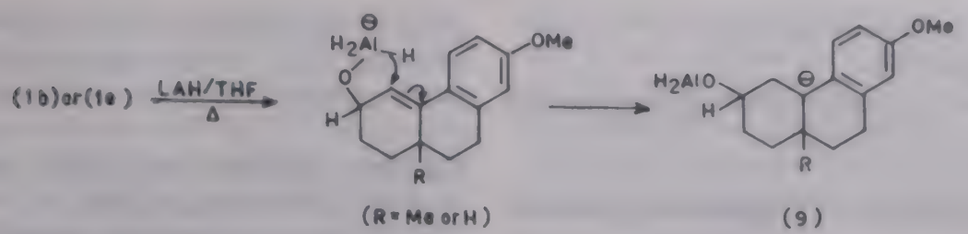
[b]This reasoning probably explains the formation of the corresponding allyl alcohols when the methoxyketones (**1b**) and (**1e**) are reduced with LAH.

[d]Alternatively the ketone **1d** gets no steric assistance from the angular methyl group (as in **1a**) for the formation of the alane intermediate necessary for better yield of the *cis*-product.

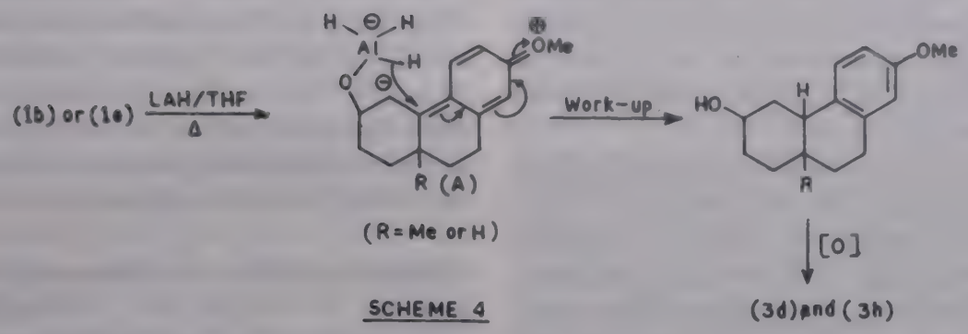
[e]The protonolysis of the alkyl C-Al bond has been shown to be stereoretentive[15] and this explains the stereospecificity observed.

[f]Less disadvantageous six-centre hydride transfer as shown in (**A**) (Scheme 4) requires less conventional addition of hydride to the styrene, and this is probably aided by the resonance effect of the methoxyl group.

[g]We thank Dr S G Biswas and Mr A Kabiraj of Department of Physics, Visca-Bharati, Santiniketan, for the results of the X-ray crystal structure analysis of **3d**.



SCHEME 3



SCHEME 4

spectra of the *cis*-ketones (**3b**) and (**3d**) exhibited angular methyl singlets at slightly lower field (δ 1.00-1.02) than those (δ 0.92) exhibited by the *trans*-isomers (**3a**) and (**3c**). The stereochemistry of the ketones, *cis*-**3b** and the *trans*-**3a** was unambiguously established from PMR spectra of the acetyl compounds (**11a**) and (**11b**) prepared respectively from **3a** and **3b**; and this would be discussed in the following paper.

Experimental Procedure

The compounds described are racemic. Melting points are uncorrected. UV spectra were recorded in ethanol on a Unicam SP 500 spectrophotometer (λ_{max} in nm), IR spectra in chloroform on a Perkin-Elmer 337 instrument (ν_{max} in cm^{-1}) and PMR spectra, unless otherwise stated, in $CDCl_3$ on a Varian T-60 spectrometer using TMS as an internal standard; chemical shift in δ (ppm). GLC was carried out on a Hewlett-Packard-5730A chromatograph using 10% UCW-982 on W.AW-DMCS (80-100 mesh. 20″ × 1/8″) column at 170° (unless otherwise stated). Extracts were dried over anhydrous Na_2SO_4 and light petroleum refers to the fraction b.p. 60-80°.

Preparation of unsaturated ketones (**1a, b**) *and* (**1d, e**)-1,2,3,9,10,11-*Hexahydro*-6,11-*dimethyl*-3-*oxophenanthrene* (**1a**)

To a stirred and ice-cold mixture of 2,7-dimethyl-1-tetralone[1] (1.52 g), dry benzene (3.3 ml) and a soln of NaOMe, prepared from Na (0.3 g) and absolute MeOH (7.3 ml), was added during 2-3 hr under N_2 a soln of methiodide, prepared from 1-diethylamino-3-butanone (0.26 g) and MeI in dry MeOH (5 ml). After stirring for 3-4 hr under ice-cold condition, the reaction mixture was refluxed for 1 hr, cooled, and acidified with H_2SO_4 (2*N*, 10 ml). The product was extracted with ether (3 × 75 ml) and the combined extract washed with water (1 × 50 ml), aq. NaOH (2*N*, 2 × 50 ml) and water and dried. Evaporation of the solvent gave an oily product (2 g) which was chromatographed over neutral alumina (100 g). Elution with benzene-light petrol (15:85) furnished the starting ketone (0.5 g). Further elution with a 60:40 mixture of benzene-light petrol provided the desired **1a** (1 g, 67% based on recovered ketone), m.p. 95-96° (ether-light petrol); IR: 1650; PMR: 7.50 (1H, *bs*), 7.10 (2H, *bs*), 6.50 (1H, *s*), 2.73-3.03 (2H, *m*), 2.42-2.63 (2H, *m*), 2.32 (3H, *s*), 1.63-2.03 (4H, *m*) and 1.18 (3H, *s*) (Found: C, 85.1; H, 8.3. $C_{16}H_{18}O$ requires C, 84.9; H, 8.0%).

1,2,3,9,10,11-*Hexahydro*-7-*methoxy*-11-*methyl*-3-*oxophenanthrene* (**1b**)

Attempted preparation of **1b** through the reported procedure[2] gave a very poor yield in our hand. It (**1b**), m.p. 85-86° (reported[2] m.p. 87°) was, therefore, prepared by a modified procedure in 38% overall yield starting from 6-methoxy-2-methyl-1-tetralone and following the procedure prescribed[3] for the related system such as **1c**.

1,2,3,9,10,11-*Hexahydro*-3-*oxophenanthrene* (**1d**)

This was prepared through the literature procedure[11]. Recrystallisation provided the pure **1d**, m.p. 82-83° (ether-light petrol or ethanol) (reported[11] m.p. 103° from ethanol); IR: 1660 (Found: C, 84.6; H, 7.3. $C_{14}H_{14}O$ requires C, 84.8; H, 7.1%).

1,2,3,9,10,11-Hexahydro-7-methoxy-3-oxophenanthrene (**1e**)

This ketone was prepared following the reported procedure[12].

Catalytic Hydrogenation of Unsaturated Ketones (1a) and (1b)

(*a*) *Reduction of* **1a** *in acid solution: formation of a stereoisomeric mixture of* 1,2,3,4,9,10,11,12-*octahydro*-6,11-*dimethylphenanthrene* (**2a, b**); *mixture of cis- and trans-ketones* (**3a, b**), *and the mixture of the* 3-*hydroxy-compounds* (**4a, b**)

A soln of **1a** (1 g) in AcOH (40 ml) and $HClO_4$ (20 drops) was hydrogenated (30 min) over Pd-C (10%, 0.3 g) at NTP. The catalyst was filtered, the filtrate neutralised with solid Na_2CO_3, extracted with ether (3 × 50 ml) and combined extract washed with water, dried, and evaporated. The oil (1 g) thus obtained was chromatographed over silica gel (30 g) column. Elution with light petrol afforded a hydrocarbon product (0.75 g, 78%) as a 90:10 mixture (GLC) of the *trans*-**2a** and *cis*-**2b** (R_t = 1.3 and 1 min respectively); b.p. 95° (bath)/0.1 mm; IR: 1615; PMR(CCl_4): 6.93-6.70 (3H, *m*), 2.96-2.60 (2H, *m*), 2.24 (benzylic Me and 1H), 1.70-1.00 (10H, *m*) and 0.73 (3H, *s*) (Found: C, 89.5; H, 10.5. $C_{16}H_{22}$ requires C, 89.7; H, 10.4%).

Further, elution of the column with ether furnished a polar material as a 1:2 mixture of ketones, *cis*-**3b** and the *trans*-**3a** (R_t = 2.4 and 3 min); and 1:5 mixture of alcohols, *cis*-**4b** and *trans*-**4a** (R_t = 3.8 and 4.7 min). Careful distillation of this mixture gave a ketonic material as a mixture (GLC) of **3a, b**, b.p. 130° (bath)/0.1 mm; IR: 1709 (Found: C, 83.9; H, 8.5. $C_{16}H_{20}O$ requires C, 84.2; H, 8.6%).

(*b*) *Reduction under neutral condition*

A soln of **1a** (0.1 g) in ethanol (10 ml) was hydrogenated over Pd-C (10%, 0.06 g). Usual work-up provided an oil (0.09 g) which was chromatographed over silica gel (7 g) column. Elution with light petrol afforded 7:93 mixture (GLC) of hydrocarbons; *cis*-**2b** and *trans*-**2a** (0.05 g, 50%); IR: 1614. Further elution with ether-light petrol (5:95) furnished a 4:6 mixture of ketones, *cis*-**3b** and *trans*-**3a** (0.04 g, 40%); IR: 1708.

(*c*) *Reduction in pyridine solution*

A soln of **1a** (0.2 g) in pyridine (20 ml) was hydrogenated over Pd-C (10%, 0.1 g). The rate of hydrogenation was very slow, and after 72 hr, the catalyst was filtered, and the soln diluted with water. The separated product was extracted with ether (3 × 25 ml), the combined extract washed with water, dil. HCl (10%) and water and dried. Evaporation of the solvent gave an oil (0.18 g, 90%), b.p. 130° (bath)/0.1 mm; IR: 1712. Analysis (GLC) of this material showed it to be a 85:15 mixture of ketones, *cis*-**3b** and *trans*-**3a**.

Catalytic reduction of allylic alcohol obtained through LAH reduction of **1a**

A soln of **1a** (0.3 g) in ether (10 ml) was added slowly to an ice-cold mixture of LAH (0.15 g) in ether (10 ml). The reaction mixture was stirred under ice-cold condition for 3 hr. Usual work-up provided a crude alcohol (0.3 g); IR: 3605. A soln of this alcohol in acetic acid and $HClO_4$ was hydrogenated as before. The product thus obtained on chromatographic purification as before furnished a product (0.14 g) as a 86:14 mixture (GLC) of hydrocarbons, *trans*-**2a** and *cis*-**2b**.

Catalytic reduction of unsaturated ketone (**1b**): *Formation of* 7-*methoxy*-11-*methyl*-1,2,3,4,9,10,11β,12α-*octahydrophenanthrene* (**2c**) *and corresponding cis-isomer* (**2d**)

A soln of **1b** (0.3 g) in AcOH and $HClO_4$ was hydrogenated over Pd-C (10%) as before. The rate of hydrogenation was found to be slower than that of **1a**. Usual work-up and chromatographic purification of the reduced product as before provided pure *trans*-hydrocarbon (**2c**) (0.15 g, 52%), b.p. 85° (bath)/0.1 mm; IR: 1610; PMR(CCl_4): 7.06-6.85 (1H, *d* J = 9 Hz), 6.38-6.70 (2H, *m*), 3.70 (3H, *s*), 1.00-2.90 (13H, *m*) and 0.72 (3H, *s*); a very weak signal at 0.93 suggested the presence of a small amount of the *cis*-isomer (**2d**) (Found: C, 83.4; H, 9.8. $C_{16}H_{22}O$ requires C, 83.4; H, 9.6%).

Lithium-liquid ammonia reduction of the unsaturated ketones (**1a, b**): (*a*) *Reduction of* **1a** *and formation of stereoisomeric mixture of* 1,2,3,4,9,10,11,12-*octahydro*-6,11-*dimethyl*-3-*oxophenanthrene* (**3a, b**)

To stirred liquid ammonia (150 ml) was added lithium metal (0.05 g). To the resulting blue-coloured soln was added dropwise during 3 min a soln of **1a** (0.3 g) in dry ether (20 ml). After addition, the reaction mixture was stirred for 10 min, and then decomposed with NH_4Cl (1.5 g). Ammonia was then evaporated, and the product dissolved in ether. Usual processing of the ether solution afforded a 65:35 mixture (GLC) of the saturated ketones (**3a, b**) (0.29 g, 96%), b.p. 140° (bath)/0.2 mm; IR; 1710; PMR(CCl_4): 6.98-6.63 (3H, *m*), 3.10-2.05 (7H, *m*) 2.26 (3H, *s*), 1.97-1.23 (4H, *m*), and two singlets at 1.00 and 0.93 for angular methyls of the *cis*-**3b** and *trans*-**3a** (Found: C, 84.2; H, 8.6. $C_{16}H_{20}O$ requires C, 84.2; H, 8.8%).

(*b*) *Reduction of* **1b** *and formation of stereoisomeric mixture of* 1,2,3,4,9,10,11,12-*octahydro-*

7-methoxy-11-methyl-3-oxophenanthrenes (**3c, d**) *and trans-3-hydroxy compound* (**4c**)

Reduction of **1b** (0.42 g) with Li-metal in liquid ammonia as above afforded an oil (0.3 g, 76%), b.p. 150-55° (bath)/0.2 mm; IR: 1710 and 1615; GLC analysis (180°) of this material indicated it to be a 63:37 mixture of ketone, viz. the *cis*-**3d** and *trans*-**3c** (R_t = 7.1 and 8.85 respectively); PMR: 7.07-6.57 (3H, *m*), 3.77 (3H, *s*), 3.10-2.30 (7H, *m*), 2.00-1.60 (4H, *m*), and two singlets at 1.00 and 0.92 respectively for the angular methyls of the *cis*-**3d** and *trans*-**3c** (Found: C, 78.6; H, 8.1. $C_{16}H_{20}O_2$ requires C, 78.7; H, 8.3%).

In another experiment, the crude reduction product (0.39 g) was chromatographed over silica gel column. Elution with ether-light petrol (7:93) gave a solid which recrystallised from light petrol (40-60°) to furnish pure *cis*-**3d**, m.p. 89-91°. Further elution with ether-light petrol (30:70) afforded an oil (72 mg) which on trituration with light petrol provided a small amount of *trans*-hydroxy compound (**4c**) as silky needles, m.p. 111-13° (light petrol, b.p. 40-60°); IR: 3690-3600; PMR (100 MHz): 7.13 (1H, *d*, *J* = 8 Hz), 6.86-6.60 (2H, *m*), 3.77 (3H, *s*), 3.97-3.60 (1H, *m*), 3.02-2.75 (2H, *m*), 2.64-2.26 (2H, *m*), 2.06-1.10 (8H, *m*) and 0.74 (3H, *s*) (Found: C, 78.1; H, 8.9. $C_{16}H_{22}O_2$ requires C, 78.0; H, 9.0%).

Reduction of unsaturated ketones (**1a, b**) *and* (**1d, e**) *with Ni-Al alloy and alkali*: (*a*) *Reduction of* **1a** *and formation of* 1,2,3,4,9,10,11β,12α-*octahydro*-6,11-*dimethyl*-3-*oxophenanthrene* (**3a**)

To a stirred soln of **1a** (0.6 g) in ethanol (37 ml) containing aq NaOH (2*N*, 37 ml) was added Ni-Al alloy (2.96 g, 50:50, BDH) portionwise during 2 hr at 25-30°. After complete addition, the reaction mixture was stirred for further 2 hr at the same temperature. The catalyst was filtered and washed with water and methylene chloride. The filtrate was diluted with water and extracted with ether-methylene chloride (4 × 60 ml). The combined organic extract was washed with water till neutral and dried. Evaporation of solvent afforded a hydroxy compound as viscous oil (0.63 g), IR: 3410-3450 (b).

Pyridinium chlorochromate[10] (0.8 g) was added in one lot to a soln of the above hydroxy compounnd (0.63 g) in dry methylene chloride (6 ml) at 25°. The resulting soln was stirred for 2.5 hr at the same temperature. Methylene chloride was decanted off, and the residue extracted with ether-methylene chloride (4 × 25 ml). The combined organic extract was washed with water (2 × 50 ml), dried and the solvent evaporated to furnish a ketonic material (0.6 g, quantitative), m.p. 93-97°; IR: 1706. GLC of this ketonic material showed it to be a 92:8 mixture of *trans*-**3a** and the *cis*-**3b**. Recrystallisation of this mixture provided the *trans*-**3a** (0.4 g, 66%), m.p. 98-100° (light petrol); further recrystallisation gave an analytical sample of **3a**, m.p. 101-2°; IR: 1705; PMR (100 MHz): 7.16-6.80 (3H, *m*), 3.16-2.16 (7H, *m*), 2.26 (3H, *s*), 2.01-1.22 (4H, *m*) and 0.92 (3H, *s*) (Found: C, 84.0; H, 8.8. $C_{16}H_{20}O$ requires C, 84.2; H, 8.8%).

(*b*) *Reduction of* **1b**: *Formation of* 1,2,3,4,9,10,11β,12α-*octahydro*-7-*methoxy*-11-*methyl*-3-*oxophenanthrene* (**3c**)

Reduction of **1b** (0.3 g) with Ni-Al alloy (1.48 g) as above afforded a crude reduced product (0.31 g). Trituration of this material with ether-light petrol furnished a small amount of 1,2,3,4,9,10,11β,12α-octahydro-3-hydroxy-7-methoxy-11-methylphenanthrene (**4c**) as silky needles, m.p. 112-14° (light petrol, b.p. 40-60°), identical with the product obtained from Li-NH_3 reduction of **1b** mentioned before (Found: C, 77.70; H, 9.1%).

Oxidation of **4c** (0.3 g) with pyridinium chlorochromate as before afforded in quantitative yield (0.3 g), m.p. 68-73° a 89:11 mixture (GLC) of ketones *trans*-**3c** and *cis*-**3d**. Recrystallisation of this mixture provided the *trans*-**3c** (0.14 g, 46%), m.p. 73-75° (light petrol). Further recrystallisation gave an analytical sample of **3c**, m.p. 76-77°; IR: 1705; PMR (100 MHz): 6.97 (1H, *d*, *J* = 9 Hz), 6.86-6.62 (2H, *m*), 3.74 (3H, *s*), 3.14-2.14 (7H, *m*), 2.04-1.44 (4H, *m*) and 0.92 (3H, *s*) (Found: C, 78.4; H, 8.4. $C_{15}H_{20}O_2$ requires C, 78.7; H, 8.3%).

(*c*) *Reduction of* **1e**: *Formation of a stereoisomeric mixture of* 1,2,3,4,9,10,11,12-*Octahydro*-7-*methoxy*-3-*oxophenanthrene* (**3g, h**)

Reduction of **1e** (0.3 g) with Ni-Al alloy and subsequent oxidation of the resulting product as before furnished an oily ketone (0.27 g). Chromatography of this product over silica gel (22 g) and elution of the column with ether-light petrol (15:85) provided a product (0.15 g, 50% overall), m.p. 105-24°, shown to be mixture, which could not be resolved on UCW or SE-30 column at 170°. Fractional crystallisation of this mixture from light petrol furnished relatively less soluble *trans*-ketone (**3g**) (0.035 g), m.p. 135-36° (lit.[12] m.p. 136-37°); IR: 1705 (Found: C, 78.0; H, 7.8. $C_{15}H_{18}O_2$ requires C, 78.2; H, 7.9%).

Mother liquor from the above crystallisations furnished a fraction which on recrystallisation gave the pure *cis*-ketone (**3h**) (0.04 g), m.p. and m.m.p. with an authentic sample, 89-91° (reported[12] m.p. 88-89°); IR: 1705 (Found: C, 78.1; H, 8.1. $C_{15}H_{18}O_2$ requires C, 78.2; H, 7.8%).

(*d*) *Reduction of* **1d**: *Formation of a stereoisomeric*

mixture of 1,2,3,4,9,10,11,12-*octahydrophenanthrenes* (**3e, f**)

Reduction of **1d** (0.38 g) with Ni-Al alloy followed by oxidation of the reduction product as before afforded a crude product, which was chromatographed over silica gel column (12 g). Elution of the column with ether-light petrol (6:94) provided a mixture (0.19 g) which could not be resolved on UCW or SE-30 column, b.p. 120° (bath)/0.1 mm; IR: 1705 (Found: C, 83.9; H, 8.1. $C_{14}H_{16}O$ requires C, 84.0; H, 8.1%).

Attempted Ni-Al alloy reduction of allyl alcohol (**7a**) *prepared from the unsaturated ketone* (**1b**)

Reduction of **1b** (0.2 g) with KBH_4 (0.07 g) following the prescribed procedure[3] afforded an oily alcohol (0.2 g) characterised as **7a** from its spectral data, IR: 3595 and 1630; PMR(CCl_4): 7.31 (1H, *d*, $J=9$ Hz), 6.63-6.46 (2H, *m*), 5.84 (1H, *d*, $J=2.5$ Hz), 4.36-4.06 (1H, *m*), 3.68 (3H, *s*), 3.11 (1H, *s*), 2.89-2.56 (2H, *m*), 2.06-1.33 (6H, *m*) and 1.01 (3H, *s*). GLC showed it to be mainly **7a** with retention time of 18.43 min.

This alcohol (**7a**) was completely recovered (from GLC and PMR) on attempted reduction with Ni-Al alloy as before.

Lithium aluminium hydride (*LAH*) *reduction of unsaturated ketones* (**1a, b**) *and* (**1d, e**): *Reduction of* **1a** *and formation of* **3b**

To an ice-cold and stirred suspension of LAH (0.25 g) in dry THF (10 ml) was added during 30 min a soln of **1a** (0.5 g) in dry THF (10 ml). The resulting reaction mixture was then heated under reflux for 6 hr, cooled, decomposed with H_2SO_4 (20 ml, 10%), and extracted with ether (3 × 50 ml). The combined ether extract was washed with water, aq. $NaHCO_3$ and water and dried. Evaporation of the solvent afforded a product which was chromatographed over silica gel (15 g) column. Elution with ether-light petrol (10:90) furnished an alcohol (0.45 g, 90%), homogeneous on GLC on a UCW column at 180°C with retention time of 3.8 min.

A soln of this alcohol (1.05 g) in dry methylene chloride (25 ml) was oxidised with pyridinium dichromate[15] (2.5 g) for 3 hr at 25°. The solvent was removed under reduced pressure, and the residue extracted with ether. The ether solution was filtered, add the residue was repeatedly washed with ether. The combined ether extract was washed with aq. $NaHCO_3$ (2 × 25 ml) and water (2 × 25 ml) and dried. Evaporation of the solvent gave a product (1 g), which was chromatographed over silica gel (36 g) column. Elution with ether-light petrol (5:95) afforded the GLC pure *cis*-ketone (**3b**) (0.85 g, 70% based on the unsaturated ketone); IR: 1708; PMR(CCl_4): 6.90-6.66 (3H, *m*), 1.15-3.00 (14H, *m*) and 1.00 (3H, *s*); MS: *m/z* 228 (M^+), 210 (M^+-18) and 195 (M^+-33).

(*b*) *Reduction of* **1b**: *Formation of* **3d**

Similar reduction of **1b** (0.3 g) with LAH as above furnished a crude hydroxy-compound (0.3 g), which was directly oxidised with pyridinium dichromate as before to give a ketonic material. Chromatography of this material over silica gel (10 g) column and elution with ether-light petrol (5:95) provided the crystalline GLC pure *cis*-ketone (**3d**) (0.16 g, 52%), m.p. 89-91° (light petrol); IR: 1710, 1610; PMR: 7.03-6.53 (3H, *m*), 3.77 (3H, *s*), 2.60-3.06 (7H, *m*), 1.40-2.00 (4H, *m*) and 1.02 (3H, *s*) (Found: C, 78.6; H, 8.2. $C_{16}H_{20}O_2$ requires C, 78.7; H, 8.3%).

(*c*) *Reduction of* **1e**: *Formation of* **3h**

Reduction of **1e** (1 g) with LAH under refluxing (13 hr) THF as before provided a mixture of products (IR: 3600 and 1710(w)). This on oxidation with pyridinium dichromate as before furnished a material (0.7 g) which was purified by column chromatography over silica gel (80 g) column. Elution with ether-light petrol (20:80) provided the saturated *cis*-ketone (**3h**) (0.3 g), m.p. 87-90°. Further, elution of the chromatogram with the same solvent mixture (1:1) afforded an alcohol (0.35 g) which on oxidation and chromatographic purification provided an additional crop of **3h** (0.2 g), and an oil. The total yield of **3h** was (0.5 g, 52%), m.p. 87-90°, identical with a sample of **3h** obtained by the Ni-Al reduction of **1e**; PMR: 7.07-6.65 (3H, *m*), 3.77 (3H, *s*) and 3.23-1.67 (12H, *m*).

In another experiment **1e** (0.5 g) was reduced with LAH under refluxing (8 hr) THF. The crude product (0.5 g) on GLC was found to be a mixture of three main products with retention times of 4.84, 7.96 and 10.93 min.

(*d*) *Reduction of* **1d**: *Formation of* **3f, 8** *and* **7b**

Reduction of (**1d**) (1 g) with LAH under refluxing (8 hr) THF afforded a product (1 g) which was chromatographed over silica gel (30 g) column. Elution with light petrol afforded the cyclopropyl derivative (**8**) as an oil (0.15 g, 16%), b.p. 100 (bath)/0.1 mm; IR: 1610; MS: *m/z* 184 (M^+); PMR (100 MHz): 7.38-6.89 (3H, *m*), 6.87-6.61 (1H, *m*), 3.14-2.45 (2H, *m*), 2.41-0.77 (10H, *m*) (Found: C, 91.1; H, 9.1. $C_{14}H_{16}$ requires C, 91.3; H, 8.8%).

Further elution of the column with ether gave an oil (0.65 g) which was directly oxidized with pyridinium dichromate as before to give a product (0.55 g); IR: 3600, 1710 and 1660. Chromatography of this product over silica gel (15 g) column and elution with ether-light petrol (5:95) provided the GLC pure *cis*-ketone (**3f**) (0.45 g, 45%) based on starting unsaturat-

ed ketone, m.p. 68-70°; IR: 1710. An analytical sample of **3f** had m.p. 75-76° (ether-light petrol) (lit.[17] m.p. 74-75°) (Found: C, 83.9; H, 8.0. $C_{14}H_{16}O$ requires C, 84.0; H, 8.1%).

Further elution of the column with pure ether afforded he allylic alcohol (**7b**) (0.18 g, 18%), m.p. 162-63° (ether); IR: 3600 (Found: C, 84.2; H, 8.83. $C_{14}H_{16}O$ requires C, 83.9; H, 8.1%). This alcohol (**7b**) on oxidation afforded the unsaturated ketone (**1d**).

Acknowledgement

We thank CSIR and UGC, New Delhi, for financial assistance.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1200-1203

Total Sythesis of a New Class of Ring-C Aromatic Steroid†

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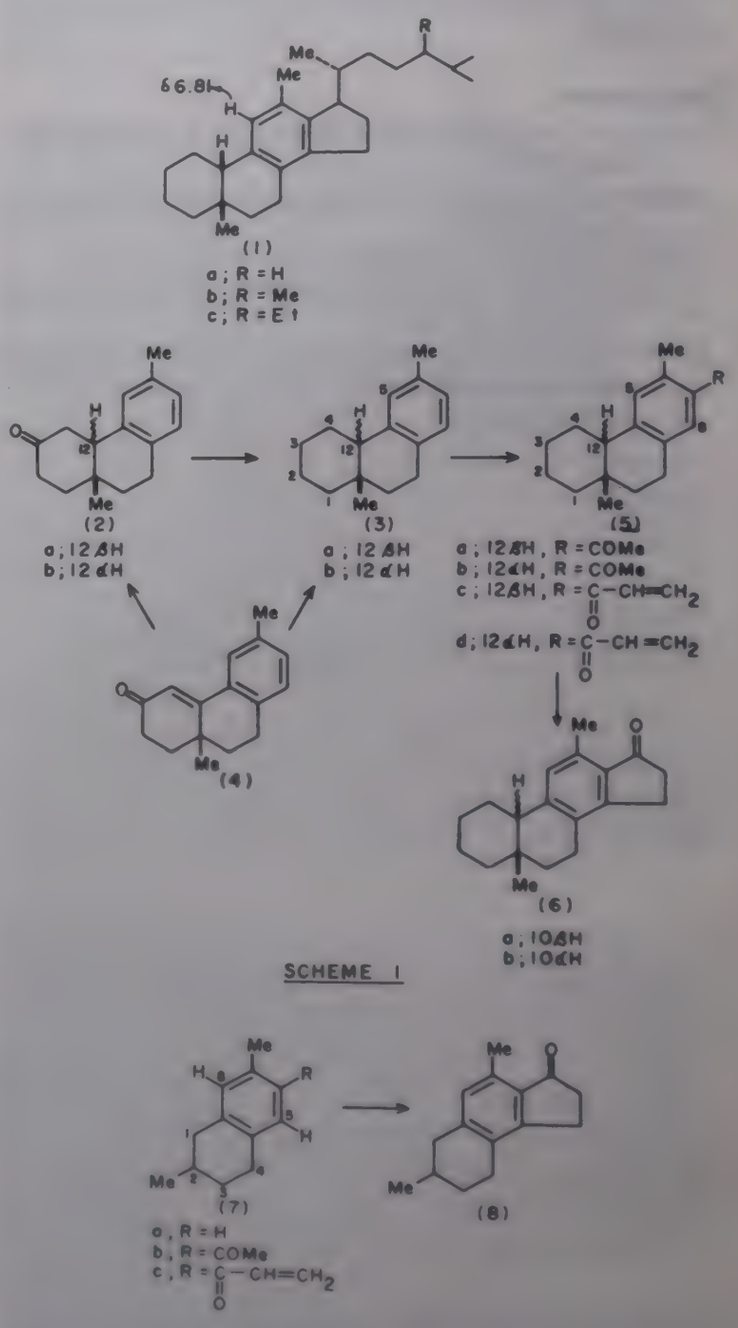
Received 28 *April* 1986; *accepted* 8 *July* 1986

The *cis*- and the *trans*-fused octahydrophenanthrene derivatives (**3a**) and (**3b**) have been elaborated to the 10βH- and 10αH-isomers, respectively, of 5,12-dimethyl-5β-gonane-8,11,13-triene-17-one. The stereochemistry of the products have been unambiguously established from PMR spectra.

Ring-C aromatic steroids have attracted the attention of many workers[1] including that of the authors[2], for such compounds have interesting pharmacological properties. The presence of partially aromatised steroidal hydrocarbons has been noticed in the geological samples (sediments and crude oils) by many workers[3]. The first identification of one such member **1a**†, having a semi-rearranged steroidal skeleton, has recently been reported by Ourisson and associates[4]. The mass spectral analysis of the monoaromatic steroid fraction also indicated the presence of higher homologues such as **1b, c**.

In the preceding paper[5] we have reported a stereospecific synthesis of the *cis*-ketone (**2a**) from the unsaturated ketone (**4**). We wish to report herein the successful transformation of **2a** to ring-C aromatic steroid (**6a**), related to **1a** isolated from geological samples (Scheme 1). The *trans*-isomer (**6b**) has also been synthesised.

Easily available 2,7-dimethyl-1,2,3,4-tetrahydronaphthalene[7] (**7a**) was selected as a model hydrocarbon for standardising the optimum conditions for its acetylation, and subsequent conversion of the acetyl derivative (**7b**) into the indanone (**8**) through the intermediate vinyl ketone (**7c**). Friedel-Crafts acetylation of **7a** in the presence of anhydrous aluminium chloride in carbon disulphide smoothly afforded, in excellent yield, the expected **7b**. The regiospecificity of this reaction was assured from the PMR spectrum of **7b** which displayed two slightly broad singlets at δ 7.32 and 6.79 assignable to C-5 and C-8 aromatic protons respectively. The crude vinyl ketone (**7c**), prepared from **7b** through Mannich base procedure, on acid-catalysed cyclisation[8] furnished in moderate yield (37%) the crystalline indanone derivative (**8**). A better overall yield (55%) of **8** was, however, realised when **7c** was prepared through a different route[9], i.e. by refluxing a mixture of **7b**, N-methylanilinium trifluoroacetate (TAMA) and paraformaldehyde in anhydrous dioxan.



Huang-Minlon reduction **2a**[5] led to the *cis*-hydrocarbon (**3a**) in high yield. Acetylation of **3a** in

*For a preliminary report on a part of this work, see Chatterjee A, Raychaudhuri S R & Chatterjee S K, *Chem Commun*, 1982, 24.

†After the completion of our work, Albrecht *et al*[10] reported that in the ring-C monoaromatic compounds (**1a, c**), the methyl group will be at C-12, and not at C-11 as previously indicated.

the presence of anhydrous aluminium chloride gave a mixture of two products (GLC), one being present as the major product; but this was not investigated further. The product obtained showed expected carbonyl band in IR, but its PMR spectrum did not exhibit any characteristic singlet for the angular methyl group. However, acetylation of **3a** under mild condition, i.e. in the presence of anhydrous stannic chloride in methylene chloride was rewarding and provided the desired acetyl derivative (**5a**)in excellent yield. In the PMR spectrum, **5a** showed two characteristic singlets at δ 6.75 and 7.25 for C-5 and C-8 aromatic protons respectively, thus proving the regiospecificity of the acetylation process. The crude vinyl ketone (**5c**), prepared from **5a**, on cyclisation with acid afforded in respectable yield the desired tetracyclic compound (**6a**).

The stereoisomeric hydrocarbon mixture containing mostly the *trans*-isomer (**3b**), obtained through hydrogenation of the unsaturated ketone (**4**) in acid solution[5], was subjected to the above sequence of reactions to furnish in moderate yield the tetracyclic *trans*-ketone (**6b**).

A mixture (65:35) of saturated ketones, *cis*-**2a** and *trans*-**2b**, available through Birch reduction of **4**[5], was also reduced by Huang-Minlon procedure to give a stereoisomeric mixture of hydrocarbons (**3a, b**). This mixture was subjected to the above series of reactions to afford a pure sample of the *cis*-ketone (**6a**), and a stereoisomeric mixture (PMR) of the tetracyclic ketones (**6a, b**).

Careful PMR study of the octahydrophenanthrene system related to **3a, b** revealed[10] that C-5 aromatic proton in the *trans*-isomer appears atlower field than does the corresponding hydrogen in the *cis*-isomer. A similar observation has been recorded in the present study also. The aromatic C-5 protons in *cis*-**5a** and *trans*-**5b** appear as broad singlets at δ 6.75 and 7.07 respectively. The C-11 aromatic protons of *cis*-**6a** and *trans*-**6b** also appear as singlets at δ 6.85 and 7.00 respectively.

Experimental Procedure

The compound described are racemic. Melting points and boiling points are uncorrected. UV spectra were recorded in ethanol on a Unicam SP500 spectrometer (λ_{max} in nm), IR spectra in chloroform on a Perkin-Elmer 337 instrument (ν_{max} in cm^{-1}) and PMR spectra, unless otherwise stated, in $CDCl_3$ on a Varian T-60 spectrometer using TMS as internal standard [chemical shift in δ (ppm)]. GLC was carried out on a Hewlett-Packard-5730A chromatograph using 10% UCW-982 on W.AW-DMCS (80-100 mesh, 20″ × 1/8″) column at 170° (unless otherwise stated). Extracts were dried over anhydrous Na_2SO_4 and light petroleum refers to the fraction b.p. 60-80°.

6-Acetyl-2,7-dimethyl-1,2,3,4-tetrahydronaphthalene (**7b**)

To an ice-cold and stirred mixture of anhydrous $AlCl_3$ (12 g) in dry CS_2 (10 ml) was added dropwise during 45 min a soln of 2,7-dimethyl-1,2,3,4-tetrahydronaphthalene[7] (**7a**) (1.2 g) and acetyl chloride (0.7 ml) in dry CS_2 (4 ml). The reaction mixture was stirred at room temperature for 2 hr and left for 16 hr. The mixture was decomposed with crushed ice, and the product extracted with ether (3 × 50 ml). The combined extract was washed with water, dried, and evaporated to furnish the desired **7b** (1.2 g, 80%), b.p. 120° (bath)/0.1 mm; IR: 1678; PMR (CCl_4): 7.32 (1H, *s*), 6.79 (1H, *s*), 2.30-3.00 (10H, *m*, including aromatic methyl and acetyl methyl), 1.25-2.10 (3H, *m*) and 1.07 (3H, *d*, *J* = 6 Hz) (Found: C, 83.0; H, 9.0. $C_{14}H_{18}O$ requires C, 83.1; H, 9.0%).

4,7-*Dimethyl*-1,2,6,7,8,9-*hexahydrobenz*[*e*]*indan*-3(*H*)-*one* (**8**): (*a*) *Through Mannich base procedure*

A mixture of **7b** (1.1 g), dry EtOH (1.5 ml), diethylamine hydrochloride (0.7 g), paraformaldehyde (0.25 g) and conc. HCl (AR, 5 drops) was refluxed for 30 min. Additional amounts of paraformaldehyde (0.25 g) and EtOH (3 ml) were added and the resulting mixture was refluxed for a further period of 16 hr. Ethanol was removed under reduced pressure, the residue made alkaline with aq. Na_2CO_3 (5 ml, 25%) and extracted with ether (3 × 75 ml). The combined extract was washed with brine, water and concentrated to afford a crude oil (1.27 g) which was converted into a crystalline methiodide in the usual way. A mixture of this methiodide (1.27 g), dry benzene (22 ml) and pyridine (2 ml) was refluxed for 22 hr. Usual work-up provided an oil which was purified by passing its soln in benzene through alumina (20 g) to furnish the vinyl ketone (**7c**) as colourless oil (0.5 g); IR; 1662; PMR (CCl_4); 7.13 (1H, *s*), 6.80 (1H, *s*), 6.78 (1H, *dd*, *J* = 10 and 17.5 Hz), 6.07 (1H, *dd*, *J* = 2.5 and 17.5 Hz), 5.79 (1H, *dd*, *J* = 2.5 and 10 Hz), 2.03-3.00 (4H, *m*), 2.35 (3H, *s*), 1.20-1.86 (3H, *m*) and 1.07 (3H, *d*, *J* = 6 Hz).

To stirred conc. H_2SO_4 (4 ml), maintained at 65-70°C, was added dropwise during 1½ hr a soln of **7c** (0.5 g) in dry light petrol (50 ml, b.p. 40-60°). A continuous flow of N_2 was maintained to sweep out the solvent so that the volume of the reaction mixture remained constant. The reaction mixture was stirred at 65-70° for a further period of 1 hr under N_2, diluted with water, and extracted with ether (3 × 50 ml). Usual processing of the organic extract furnished the desired **8** (0.42 g, 37% based on **7b** used), m.p. 111-

13°. Recrystallisation provided an analytical sample of **8**, m.p. 114-15° (ether-light petrol); IR: 1692; PMR: 6.79 (1H, *s*), 2.00-3.10 (8H, *m*), 2.57 (3H, *s*), 1.26-1.93 (3H, *m*) and 1.07 (3H, *d*, J = 6 Hz) (Found: C, 84.3; H, 8.6. $C_{15}H_{18}O$ requires C, 84.1; H, 8.5%).

(b) Through a new route for preparation of vinyl ketone (**7c**)

A magnetically stirred mixture of **7b** (0.6 g), paraformaldehyde (0.3 g) and N-methylanilinium trifluoroacetate (TAMA)[9] (0.75 g) in dry dioxan (4 ml) was refluxed under N_2 for 3 hr. The mixture was cooled and additional amounts of paraformaldehyde (0.18 g), ml). The aqueous layer was saturated with sodium acet- reaction mixture was refluxed for further 2 hr. It was diluted with water and extracted with ether (3 × 50 ml). The aqueous layer was saturated with sodium acetate and again extracted with ether (2 × 50 ml). Usual processing of the combined organic extract afforded **7c**, which was purified as before to furnish pure **7c** (0.45 g), b.p. 130° (bath)/0.1 mm. This compound on cyclisation with acid as before afforded the indanone derivative (**8**), m.p. and m.m.p. 111-13° in better yield (0.35 g, 55% based on **7b** used).

6,11-*Dimethyl*-1,2,3,4,9,10,11β,12β-*octahydrophenanthrene* (**3a**)

A mixture of *cis*-ketone (**2a**) (0.2 g), dry diethylene glycol (16 ml), KOH (4 g) and hydrazine hydrate (99%, 1.6 ml) was refluxed under N_2 for 1 hr. The water formed was removed until the temperature of the reaction mixture rose to 180°. The reaction mixture was heated for further 4 hr in an oil-bath maintained at 200°, diluted with ice-water and HCl, and extracted with ether (3 × 50 ml). The combined extract was washed with water, dried and evaporated to furnish the desired **3a** as an oil (0.15 g, 81%), b.p. 120° (bath)/0.2 mm; IR: 1612; PMR(CCl_4): 6.73 (3H, *m*), 2.90-2.57 (2H, *m*), 2.22 (3H, *s*), 2.45-1.70 (1H, *m*), 1.70-1.20 (10H, *m*) and 0.88 (3H, *s*); the homogeneous nature was also established through GLC. (Found: C, 89.3; H, 10.1. $C_{16}H_{22}$ requires C, 89.7; H, 10.4%).

7-*Acetyl*-6,11-*dimethyl*-1,2,3,4,9,10,11β,12β-*octahydrophenanthrene* (**5a**)

To a cold (−10°C) and stirred soln of **3a** (0.6 g) and acetyl chloride (0.6 ml) in dry CH_2Cl_2 (3 ml) was added dropwise during 30 mm a soln of stannic chloride (0.36 ml) in CH_2Cl_2 (4 ml). The reaction mixture was stirred at −10°C for 2 hr more, and decomposed with cold dil. HCl. Usual work-up with ether afforded a dark green oil which was purified by passing its benzene soln through a column of alumina (20 g). Evaporation of the solvent provided the desired **5a** (0.55 g, 76%), b.p. 120° (bath)/0.1 mm; IR: 1680; PMR(CCl_4): 7.25 (1H, *s*), 6.75 (1H, *s*), 2.92-2.67 (2H, *m*), 2.43 (3H, *s*), 2.40 (3H, *s*), 2.30-2.15 (1H, *m*), 1.87-1.25 (10H, *m*) and 0.87 (3H, *s*) (Found: C, 84.2; H, 9.7. $C_{18}H_{24}O$ requires C, 84.3; H, 9.4%).

5,12-*Dimethyl*-10α*H*-5β-*gonane*-8,11,13-*triene*-17-*one* (**6b**)

A 90:10 mixture (1 g) of *trans*-**3b** and *cis*-**3a**, obtained from catalytic reduction of **4** in acid soln, was acetylated in the presence of stannic chloride as before to furnish the practically pure acetyl compound (**5b**) (0.9 g, 75%), b.p. 125° (bath)/0.1 mm; IR: 1678; PMR: 7.43 (1H, *s*), 7.07 (1H, *s*), 3.07-2.66 (2H, *m*), 2.55 (3H, *s*), 2.49 (3H, *s*), 2.40-2.20 (1H, *m*), 1.80-1.20 (10H, *m*) and 0.73 (3H, *s*); a very weak signal at δ 0.87 indicated the presence of a trace of the *cis*-isomer (**5a**).

Compound (**5b**, 0.9 g) was converted into the vinyl ketone (**5d**) by the reported procedure[9] described above. The only modification was that the refluxing was done for a longer period, i.e. 9 hr. The crude **5d** (0.6 g) had the following spectral characteristics: IR: 1675; UV: 263 (ε 9,454); PMR: 7.11 (1H, *s*), 6.95 (1H, *s*), 6.77 (1H, *dd*, J = 10 and 17 Hz), 6.08 (1H, *dd*, J = 3 and 17 Hz), 5.76 (1H, *dd*, J = 3 and 10 Hz), 3.00-2.66 (2H, *m*), 2.37 (3H, *s*), 2.17-2.33 (1H, *m*), 2.03-1.20 (10H, *m*) and 0.73 (3H, *s*).

The crude **5d** (0.6 g) on cyclisation with acid as before furnished initially a gummy solid which recrystallised from light petrol to afford pure **6b** (0.4 g, 42% based on **5b**), m.p. 124-25°; IR: 1688; UV: 263 (ε 18,750); PMR: 7.00 (1H, *s*), 2.57 (3H, *s*), 2.50-2.90 (5H, *m*), 1.00-2.40 (12H, *m*) and 0.73 (3H, *s*); MS: m/e 268 (M^+, base peak), 253 (M^+—CH_3), 240 (M^+—CO) and 225 (M^+—43) (Found: C, 85.0; H, 9.0. $C_{19}H_{24}O$ requires C, 85.0; H, 9.0%).

The acetyl compound (**5b**) (0.5 g) was converted into the vinyl ketone (**5d**) (0.3 g) through the Mannich base procedure mentioned before. Cyclisation of **5d** afforded the pure *trans*-**6b** in better yield (0.28 g, 53%), m.p. 122-24°.

5,12-*Dimethyl*-10β*H*-5β-*gonane*-8,11,13-*triene*-17-*one* (**6a**)

The *cis*-acetyl derivative (**5a**) (0.37 g) was converted into the corresponding vinyl ketone (**5c**) (0.23 g), which on acid cyclisation furnished the pure *cis*-**6a** (0.16 g, 42% overall), m.p. 115-16° (light petrol); IR: 1688; PMR: 6.80 (1H, *s*), 2.58 (3H, *s*), 2.50-2.90 (5H, *m*), 2.40-100 (12H, *m*) and 0.88 (3H, *s*) (Found: C, 84.9; H, 9.0. $C_{19}H_{24}O$ requires C, 85.0; H, 9.0%).

Acknowledgement

We thank the CSIR, New Delhi and East India Pharmaceutical Works Ltd, Calcutta for financial assistance.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1204-1208

Electrophilic Substitution of Indoles: Part IX—Reaction of Indoles with Iminium Systems

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Received 2 *June* 1986; *accepted* 27 *June* 1986

The electrophilic substitution of indoles with iminium systems has led to the synthesis of new and interesting heterocyclic compounds, the structures of which have been settled from detailed ^1H and ^{13}C NMR studies.

The electrophilic substitution reactions of indoles with carbonyl systems in the presence of Lewis acids have been investigated extensively in our laboratory[1-8] in a programme on the synthesis of biodynamic indole compounds. Of special significance has been our work with the simple molecule like acetone. This molecule constitutes one of the most complex, yet fascinating electrophiles for study. It can be used to prepare the propenyl system[2]. Multiple carbon units containing six and nine carbons can also be generated *in situ* for building up the desired macrocyclic rings[2-8]. We had been interested in extending these reactions to iminium systems. Just as a polarised carbonyl compound is sufficiently electrophilic to attack the indole system, as also the carbon-nitrogen double bond as in an iminium system, particularly when the nitrogen atom bears a full positive charge, is also expected to be an effective electrophile towards this heterocyclic nucleus. We were able to effectively polarise the carbon-nitrogen double bond by coordinating the nitrogen to the electron deficient boron in $BF_3.Et_2O$. Our earlier exploration[9] in this area with indole and benzaniline provided a new and interesting trimer (**1**).

In this paper we report the results of our investigation with various imine systems, viz. 4-chloro-3′-nitro, 4-chloro-4′-nitro- and *o*-hydroxybenzylidenanilines with indoles. With 4-chloro-3′-nitrobenzylideneaniline a new trimeric product (**2**), similar to the trimer (**1**), was obtained (Chart 1). However, in this case the corresponding monomer (**3**) and the dimer (**4**) could not be isolated from the reaction mixture as was achieved earlier[9]. This was possibly because the nitro group deactivated the ring thereby making the benzylidene carbon more prone to nucleophilic attack.

Trimer (**2**), m.p. 307° (EtOH), $C_{34}H_{27}N_5O_4$ (M^+ 617), revealed the presence of three indole ≥NHs at σ 10.83 (bs) and twenty aromatic protons as a multiplet in the region σ 6.52-8.00 in its 80 MHz PMR spectrum. Two benzylic methines were evident at σ 5.89 and σ 5.77 (1H, *s* each). The structure of this product was unambiguously confirmed as **2** from a detailed analysis of its ^{13}C NMR spectrum (Fig. 1). The isolation of such trimers (**1**) and (**2**) is significant for these could better explain the formation of compound (**5**) synthesised by Bergmann having the 3-CH_2-3′, 2′-CH_2-3″,2″-CH_2-2 linkage rather than an intermediate (**6**) with an unsubstituted C_3-position.

4-Chloro-4′-nitrobenzylideneaniline afforded the dimer (**7**, d.p. 230° (petrol-benzene), M^+ 367 ($C_{23}H_{17}N_3O_2$). From its PMR (vide Experimental) and ^{13}C NMR analyses (Fig. 1) it was identified as 4-nitro-diindolylmethane [lit[10] d.p. 225° (ethyl acetate-petrol)].

o-Hydroxybenzylideneaniline reacted with indole to afford a new indolo[2-3,*b*]carbazole system (**8a**) in addition to the 2′-hydroxyphenylindolyl-3-methane (**9**). The structure of the third product (**10**) which was obtained in a small amount is under investigation.

Compound (**9**), $C_{23}H_{18}N_2O$ (M^+ 338), m.p. 190-200° (petrol-benzene), was isolated by column chromatography over silica gel. Its 80 MHz PMR spectrum revealed the presence of two indole ≥NHs at σ 10.69 as a broad singlet. This broadness indicated coupling with the adjacent C-2 protons. The phenolic hydroxyl group appeared at σ 9.35 while the multiplet in the aromatic region (σ 6.74-7.31) integrated for fourteen protons. The methine proton resonated as a singlet at σ 6.20. The ^{13}C NMR spectrum (both decoupled and SFORD) could be readily explained on the basis of structure (**9**) for the compound (Fig. 1). Literature survey revealed that an identical compound, d.p. 349° (benzene-petrol), had been reported[10]. No

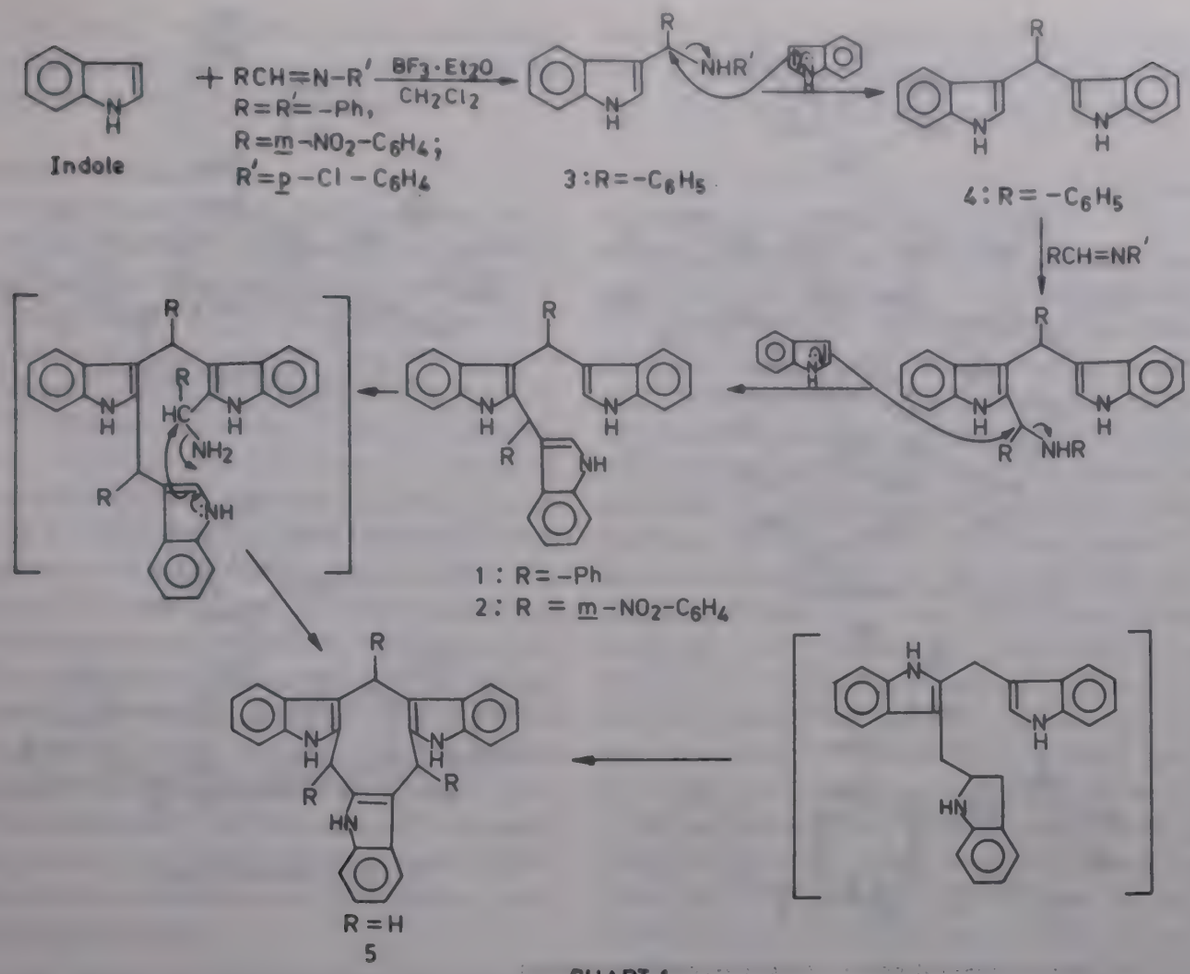


CHART-1

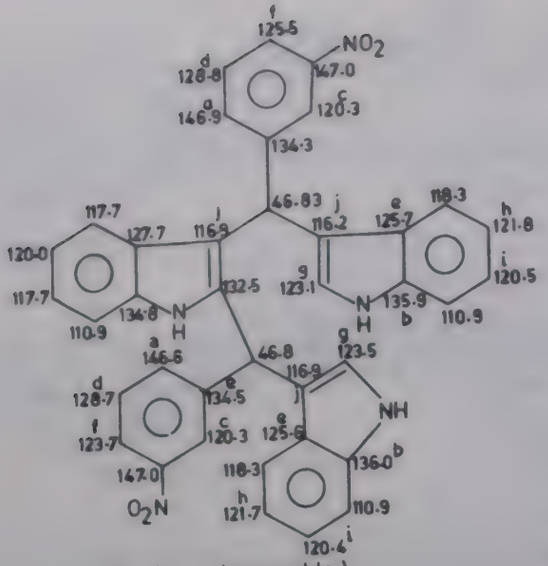
further data was available in the literature besides the melting point.

The molecular ion peak at *m/z* 442 in the mass spectrum of **8a**, m.p. > 300° (acetone) indicated its dimeric structure. The appearance of half of the total number of protons in the PMR spectrum confirmed the presence of a symmetrical molecule. The indole >N*H* appeared at σ 10.34 as a sharp singlet. Absence of coupling confirmed that the C-2 positions of both the indole nuclei must therefore be substituted. The singlet at σ 9.78 (disappearing on deuteration) was assigned to the phenolic −O*H*. The aromatic protons resonated as a multiplet in the region σ 7.31-6.35. From mechanistic considerations two structures (**8a**) and (**8b**) were possible (Chart 2) for the product. However, in case of structure (**8a**) the methine protons would resonate in the same magnetic field and exhibit identical chemical shifts but in structure (**8b**) they would be expected to show different shifts. The very fact that the methine protons appeared as a singlet at σ 6.15 confirmed the structure of the product as **8a**. This structure possesses a centre of symmetry. The proposed structure (**8a**) received further confirmation from its 25 MHz ^{13}C NMR spectrum (Chart 2). Fifteen carbon signals could be clearly seen in the plot expansion. The methine carbon appeared at 31.3 ppm. The dielectric polarization transfer (DEPT) spectrum was studied at 100°. In such a polarisation transfer experiment only the protonated carbons could be seen. Moreover the presence of only one sharp CH resonance at 31.3 ppm at 100° confirmed the structure of the product to be **8a** having the higher symmetry.

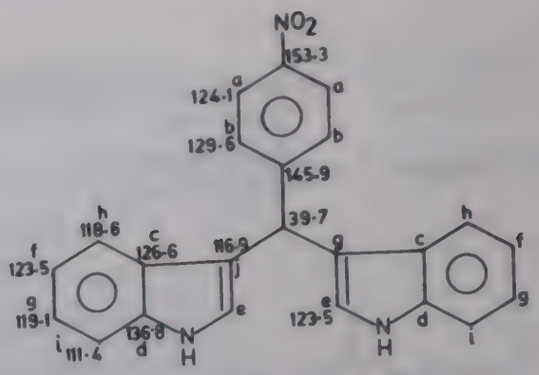
As a result of the interesting observations made with indole and various imine systems these investigations were extended to 2-methylindole. However, in this case the reaction stopped at the diindolylmethane stage as was observed with benzalaniline, *o*-hydroxybenzylideneaniline and *p*-bromo-*o*-hydroxybenzylideneaniline. With 4-chloro-4′-nitrobenzalaniline and 4-chloro-3′-nitrobenzalaniline no products could be isolated from the reaction mixture.

2-Methylindole reacted with benzalaniline to give a single product (**11**), m.p. 223° (petrol-benzene), $C_{25}H_{22}N_2$ (M^+ 350). With *o*-hydroxybenzylideneaniline and *p*-bormo-*o*-hydroxylbenzylideneaniline the same dimer (**12**), m.p. 191-92° (petrol-benzene), was obtained. The structures of the products were confirmed from their ^{13}C NMR data (Fig. 1).

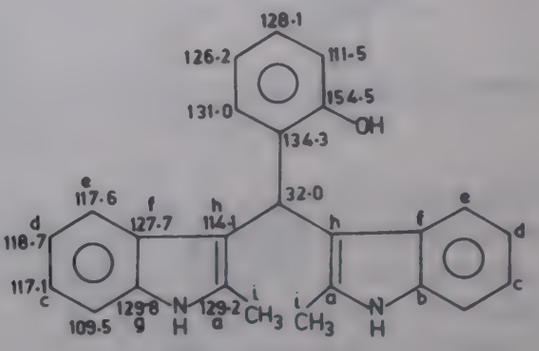
No free aldehyde could be detected in any of the reaction mixtures throughout the course of this inves-



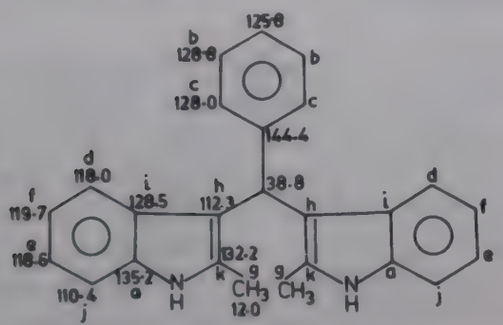
2 : (a–j : exchangeable)



7 : (a–i : identical pairs)

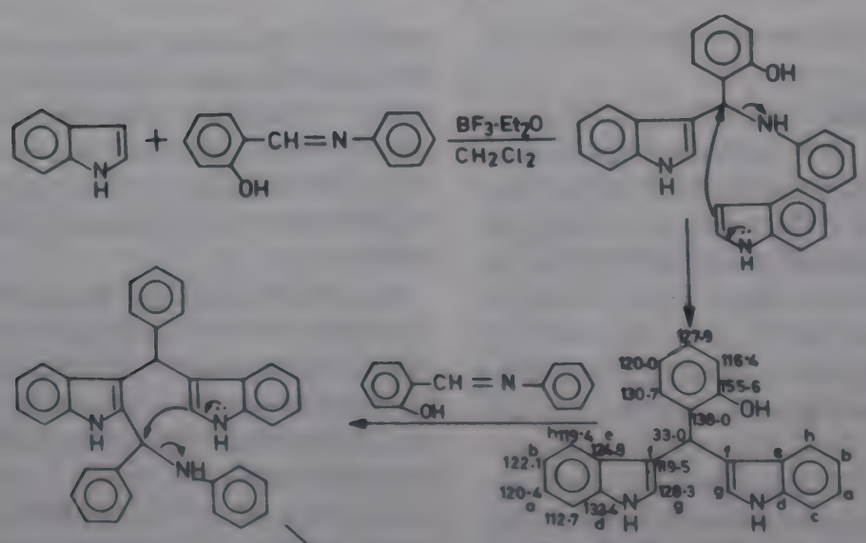


12 : (a–i : identical pairs)

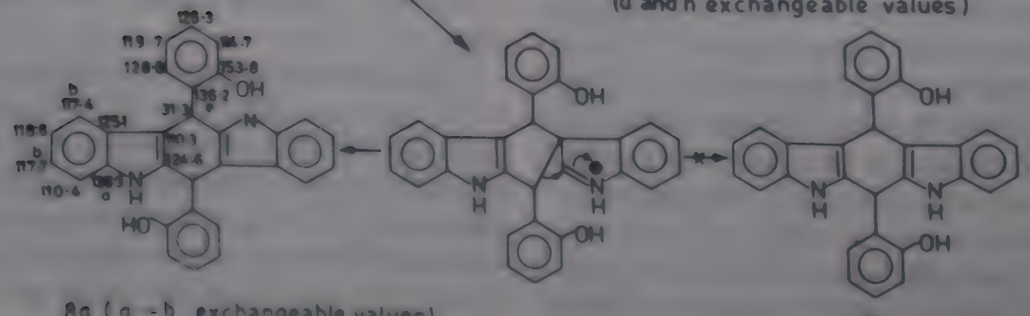


11 (a–k : identical pairs) (e & a exchangeable values)

Fig 1



9 a–h identical pairs
(a and h exchangeable values)



8a (a – b exchangeable values)

8b

CHART 2

tigation when blank experiments were performed thereby confirming that the imine systems did not decompose under the reaction conditions.

Experimental Procedure

The melting points were recorded in a Koflet block and are uncorrected. The UV spectra were recorded on a Varian Techtron 634 spectrophotometer in 95% aldehyde-free ethanol, (λ_{max} in nm; the figures within brackets refer to log ε values); the infrared spectra in KBr (ν_{max} in cm^{-1}) using Beckmann IR 20, Pye Unicam SP1025 infrared and Perkin-Elmer 782 spectrophotometers; the PMR spectra (chemical shifts in σ-scale downfield from TMS internal standard) were recorded using FT-80A, XL-200, XL-300 and XL-400 spectrometers; and the ^{13}C NMR spectra on XL-300 (75 MHz) and FT 80A (20 MHz) NMR spectrometers. The solvent used was DMSO-d_6. Rotations were measured in a Perkin-Elmer model 241 electronic polarimeter and the mass spectra on AEI MS 3074 and Hitachi RMU 61 spectrographs. The purity of the reactants, where necessary, was checked by GLC (GCV Chromatograph, Pye-Unicam). All the reactions were carried out under nitrogen atmosphere. 2-Methylindole was synthesised in 70% yield according to the literature report[11].

Column and thin layer chromatographic analyses were carried out using Brockmann alumina (grade-basic) and silica gel [BDH (60-120 mesh)] respectively. Preparative TLC was carried out on plates coated with silica gel G (Merck). The spots were detected in an iodine chamber. The analytical samples were routinely dried *in vacuo* over P_2O_5 for 24 hr. Anhydrous sodium sulphate was used to dry the organic solvents. Petrol refers to petroleum ether b.p. 60-80°. The yields were calculated on the basis of the pure isolated product obtained.

Reaction of indole with 4-chloro-3′-nitrobenzylideneaniline Formation of the trimer (**2**)

To a solution of 4-chloro-3′-nitrobenzalaniline (1.1g) in dry methylene chloride (15 ml) at 0° boron trifluoride etherate (0.5 ml) was added followed by the dropwise addition of indole (0.5 g) in dry methylene chloride (10 ml). The reaction mixture was stirred for 18 hr, poured over ice chips and extracted with methylene chloride. The organic layer was washed with 2% aq $NaHCO_3$, water and dried. The concentrate on chromatography over siliva gel afforded **2** in the benzene eluate; $[\alpha]_D^{21} = \pm 0°$ (EtOH); m.p. 307° (ethanol); R_f = 0.5 (benzene-ethyl acetate[1], 9:1); yield 15% (based on product isolated) (Found: C, 73.8; H, 4.4; N, 11.3. $C_{38}H_{27}N_5O_4$ requires : C, 73.9; H, 4.4; N, 10.7%); UV (EtOH): 220 (4.74) and 272 (4.18); (50% $HClO_4$/EtOH); 204 (4.52), 218 (4.49) and 262 (4.26); IR: 3400, 1535, 1460, 1355, and 750; MS: *m/z* 617 (M^+) 599 (M^+-O), 557 (M^+-2NO), 495 (M^+-$C_6H_4NO_2$), 367, 245 and 117 (100%).

Reaction of indole with 4-chloro-4′-nitrobenzylideneaniline-Isolation of compound (**7**)

To a solution of indole (1 g) in dry methylene chloride (20 ml), 4-chloro-4′-nitrobenzylideneaniline (2.2 g) in methylene chloride was added followed by dropwise addition of boron trifluoride etherate (1.2 ml). Stirring was continued for 8 hr, the reaction mixture poured over ice chips and extracted with methylene chloride. The organic layer was washed with 2% aq $NaHCO_3$, water, dried and the residue chromatographed over silica gel to give compound (**7**) in the benzene eluate; $[\alpha]_D^{21°} = \pm 0°$ (EtOH); d.p. 230° (petrol-benzene) [lit[17] d.p. 225[D] (ethyl acetate-petrol)]; R_f = 0.54 (benzene); yield 40% (Found: C, 75.3; H, 4.7; N, 11.4. Calc for $C_{23}H_{17}N_3O_2$ C, 75.2; H, 4.6; N, 11.44%); UV (EtOH): 223 (4.79), 275 (4.35) and 290 (4.26); + (50% $HClO_4$/EtOH): 203 (4.41), 221 (4.30), 261 (4.31) and 308 (4.06); IR: 3420, 1600, 1510, 1460, 1350 and 750; 80 MHz PMR: δ 10.11 (2H, bs), 8.18 (2H; *d*, *J* = 9.0), 7.62 (2H, *d*, *J* = 8.0), 7.50-6.84 (10H, *m*) and 6.94 (1H, *s*); 20 MHz ^{13}C NMR: 153.3 (*s*, C-14), 145.9 (*S*, C-1′), 136.8 (*S*, C-9 + C-9′), 129.6 (*d*, C-12 + C-16), 126.6 (*S*, C-4 + C-4′), 124.1 (*d*, C-13 + C-15), 123.5 (*d*, C-2 + C-2′), 121.3 (*d*, C-6 + C-6′), 119.1 (*d*, C-7 + C-7′), 118.6 (*d*, C-5 + C-5′), 116.9 (*S*, C-3 + C-3′); 111.8 (*d*, C-8 + C-8′), 39.7 (*d*, C-10); MS: *m/z* 367 (M^+), 337 (M^+—NO); 245 (M^+-$C_6H_4NO_2$; 100%) and 117.

Reaction of indole with o-hydroxybenzylideneaniline: Isolation of compounds (**8a**), (**9**) *and* (**10**)

To a solution of *o*-hydroxybenzylideneaniline[12] (1.5 g) in dry methylene chloride (20 ml) at 0° boron trifluoride etherate (1.2 ml) was added dropwise, followed by the addition of a solution of indole (1g) in dry methylene chloride (10 ml). Stirring was continued for 8 hr, the reaction mixture poured over crushed ice and extracted with methylene chloride. The organic layer was washed with 2% aq $NaHCO_3$, water, dried, concentrated and the solid obtained recrystallised from petrol-benzene to afford pure **10** as a yellow crystalline solid, m.p. 224-25°; yield 30%; R_f = 0.3 (benzene). This compound is under investigation.

The mother liquor upon concentration and chromatography over silica gel afforded compounds (**9**) and (**8a**) in the benzene and benzene-ethyl acetate (9:1) eluates respectively.

Compound (**9**). $C_{23}H_{18}N_2O$ (M^+ 338); m.p. 199-200° (petrol-benzene) [lit.[17] d.p. 349° (petrol-benzene)]; $[\alpha]_D^{21°} = \pm 0°$ (EtOH); R_f = 0.48 (benzene - ethyl acetate, 9:1); yield 25% (Found: C, 81.4; H, 5.4; N,

8.2. $C_{23}H_{18}N_2O$ requires C, 81.7; H, 5.3; N; 8.3%); UV EtOH): 226 (4.74), 282 (4.10) and 291 (403); + 50% $HClO_4$: 205 (4.48), 256 (4.26), 262 (4.26) and 321 (4.29); IR: 3400, 1600, 1500, 1450, 1330, 1270 and 740; MS: *m/z* 338 (M^+), 245 (M^+-C_6H_4OH), 219 (H^+-Indolyl + − H; 100%) and 117.

Compound (**8a**), m.p. > 300° (acetone), R_f = 0.36 (benzene-ethyl acetate, 9:1); yield 15% (Found: C, 81.7; H, 5.1; N, 6.3, $C_{30}H_{22}N_2O_2$ requires : C, 81.4; H, 5.0, N, 6.3 %); UV (EtOH): 291 (4.18), 281 (4.37), 228 (4.84) and 210 (4.76); + 50% $HClO_4$: 325 (4.08), 275 (4.32) and 215 (4.62); IR: 3495, 3420, 1595, 1460, 1335, 1270 and 750; MS: *m/z* 442 (M^+), 440 (M^+-2H; 100%), 349 (M^+-C_6H_4OH) and 256.

Reaction of 2-methylindole with benzalaniline: Isolation of compound (**11**)

To a cooled (0°C) solution of benzalaniline (1.5 g) and boron trifluoride etherate (1.2 ml) in dry methylene chloride was added dropwise a solution of 2-methylindole (1 g) in dry methylene chloride (10 ml). The mixture was stirred (12 hr) under a nitrogen blanket, poured over crushed ice and extracted with methylene chloride. The organic layer was washed with 2% aq. $NaHCO_3$, water and dried. The concentrate on chromatography afforded compound (**11**) in the petrol-benzene (1:1) and benzene eluates; $[\alpha]_D^{21°}$ = ± 0° (EtOH); R_f = 0.45 (benzene); yield 60%; (Found: C, 85.5; H, 6.5; N, 7.9. $C_{25}H_{22}N$ requires C, 85.7; H, 6.3; N, 8.0 %); UV (EtOH): 210 (4.68), 228 (4.73), 284 (4.12) and 292 (4.07); + 50% $HClO_4$: 212 (4.04), 239 (4.13), 263 (4.17) and 310 (3.86); IR: 3430, 1610, 1575, 1505 and 760; 80 MHz PMR: δ 10.67 (2H, *m*, indole ≥NH), 7.32-6.63 (13H, *m*, aromatic protons), 5.89 (1H, *s*, methine proton), 2.03 (6H, *s*, indolyl methyls); MS: *m/z* 350 (M^+), 335, 273, 237, 218 (base peak) and 130.

Reaction of 2-methylindole with o-hydroxybenzylideneaniline: Isolation of compound (**12**)

To a solution of *o*-hydroxybenzylideneaniline (1.5 g), and boron trifluoride etherate (1.2 ml) in dry methylene chloride (20 ml) was added with stirring a solution of 2-methylindole (1 g) in dry methylene chloride (10 ml). Stirring was continued for 9 hr, the reaction mixture poured over crushed ice and extracted with methylene chloride. The organic extract was washed with 2% aq $NaHCO_3$, water, dried and chromatographed over silica gel. The benzene eluate afforded compound (**12**), m.p. 199-200° (benzene), $[\alpha]_D^{21°}$ ± 0° (EtOH), R_f = 0.6 (benzene-ethyl acetate, = 4.1; yield 30% (Found: C, 81.6; H, 6.1; N, 7.5; $C_{24}H_{22}N_2O$ requires C, 82.0; H, 6.0; N, 7.7 %); UV (EtOH): 209 (4.58), 228 (4.69), 282 (4.14) and 291 (4.06); + 50% $HClO_4$: 210 (4.05), 218 (4.03), 267 (3.85) and 315 (3.65); IR: 3510, 3420, 1635, 1575, 1470, 1315, 1285 and 750; 80 MHz PMR: 11.30 (2H, *s*, indole NH), 9.84 (1H, *s*, phenolic OH), 7.98-7.27 (12H, *m*, aromatic protons), 6.80 (1H, *s*, methine proton) and 2.74 (6H, *s* indolyl methyls); MS: *m/z* 366 (M^+, base peak), 351, 220 and 130.

Reaction of 2-methylindole with p-bromo-o-hydroxybenzylideneaniline: Isolation of compound (**12**)

To a solution of *p*-bromo-*o*-hydroxybenzylideneaniline (3 g) in dry methylene chloride (20 ml) was added boron trifluoride etherate (1.2 ml) at 0°. Followed by dropwise addition of 2-methylindole (1 g) in dry methylene chloride (15 ml), with stirring (18 hr). The reaction mixture was poured over crushed ice, extracted with methylene chloride, washed with 2% aq $NaHCO_3$, water dried and chromatographed. The benzene eluate afforded **12**; yield 45% based on the product (isolated).

Acknowledgement

The authors thank Dr S C Pakrashi, Director, Indian Institute of Chemical Biology, Jadavpur, Mr A K Acharya, Mr J Ghosh and Mr P Ghosh of the Organic Instrumentation Laboratory, Chemistry Department, Calcutta University for spectral measurements, and to the UGC, New Delhi (M S and A K D), CCRAS (New Delhi) (R.C.), and DSt (New Delhi) (U K P) for financial assistance.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1209-1213

Synthesis of Isoxazolyltetrazoles

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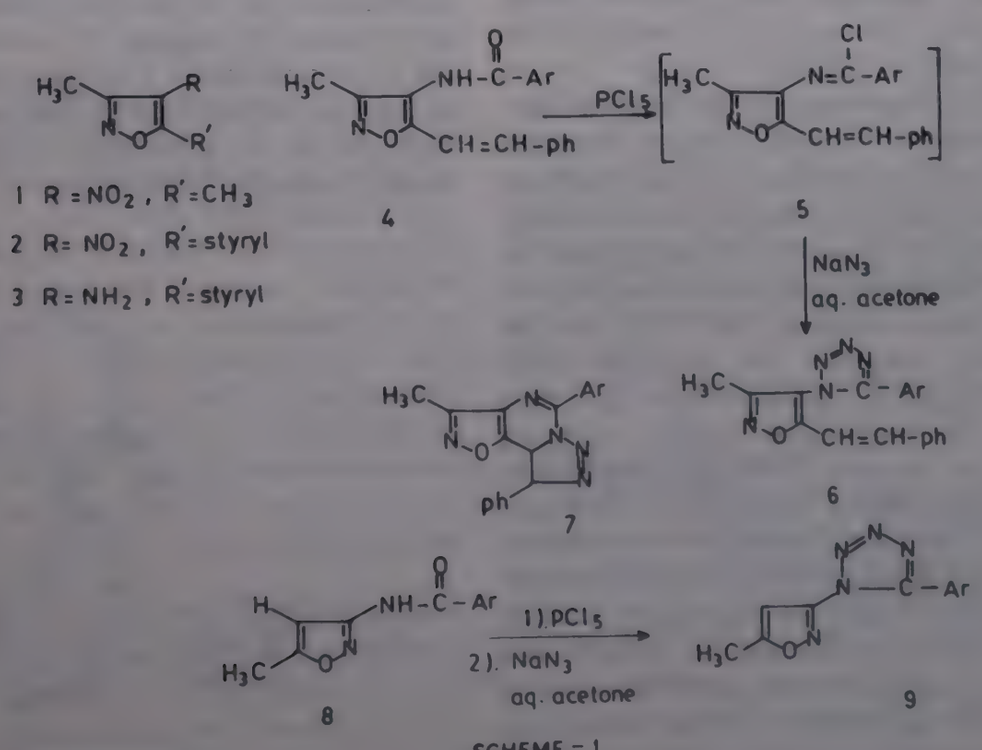
Received 13 *January* 1986; *revised and accepted* 30 *June* 1986

Isoxazolyltetrazoles **6** and **9** have been synthesized by the reaction of 4-aroylamino- and 3-aroylaminoisoxazoles (**4** and **8**) with phosphorous pentachloride and azidolysis of the resulting imidoyl chlorides, respectively. The structures of these tetrazoles have been established by their elemental analyses and spectral data (IR, PMR, mass).

The interaction of schiff bases derived from aminoisoxazoles has been studied earlier by us with a variety of reactive substances such as nitrile oxides[1], tetracyanoethylene[2], chloroketene[3], chlorosulphonyl isocyanate[4] and mercaptoacetic acid[5]. In continuation of our interest in the derivatives of aminoisoxazoles we have now chosen acylaminoisoxazoles for the synthesis of the title compounds.

Regiospecific styrylation of 3,5-dimethyl-4-nitroisoxazole (**1**)[6] under Knoevenagel conditions followed by reduction of the nitro group with $SnCl_2$-HCl gave 4-amino-3-methyl-5-styrylisoxazole (**3**). Interaction of **3** with different acid chlorides furnished the required acylaminoisoxazoles (**4**)[7]. These isoxazole-anilides when heated with PCl_5 gave the reactive imidoyl chlorides (**5**) which were not isolated. After the removal of $POCl_3$ under reduced pressure, the azidolysis of **5** was carried out in acetone medium with sodium azide and aq. sodium acetate to give the isoxazolyltetrazoles **6** (Scheme 1).

The reaction is likely to produce isoxazolyltetrazole (**6**)[8] and/or **7**, a fused tricyclic heterocycle, which is expected to result from an internal 1,3-dipolar cycloaddition of the azide to the styryl double bond. The latter possibility may be considered because of the propensity of the styryl double bond to act as a dipolarophile[9,1]. However, the elemental analysis and spectral data showed the product of azidolysis to be 5-aryl-1-(3-methyl-5-styryl-4-isoxazolyl)tetrazoles (**6**; Table 1). The strong evidence in favour of this structure, is the appearance of an *AB* quartet ($J = 15$ Hz) due to the two ethylenic protons of the styryl double bond in the PMR spectra of **6**. Had the ethylenic bond been involved in the reaction, the two



SCHEME - 1

Table I—Physical and Analytical Data of 4-Acylaminoisoxazoles (4) and 5-Aryl-1-(3-methyl-5-styryl-4-isoxazolyl)tetrazoles (6)

Compd	Ar	4-Acylaminoisoxazoles (4)					Isoxazolyltetrazoles (6)†				
		m.p. °C	Mol. formula	Found (%) (Calc.)			m.p. °C	Mol. formula	Found (%) (Calc.)		
				C	H	N			C	H	N
a	Phenyl*	—	—	—	—	—	168‡	$C_{19}H_{15}N_5O$	69.1 (69.3	4.5 4.6	21.2 21.3)
b	*p*-Tolyl	182	$C_{20}H_{18}N_2O_2$	75.3 (75.5	5.6 5.7	8.8 8.8)	165‡	$C_{20}H_{17}N_5O$	69.9 (70.0	4.9 5.0	20.4 20.4)
c	Methyl*	—	—	—	—	—	175‡	$C_{14}H_{13}N_5O$	62.9 (62.9	4.8 4.9	26.1 26.2)
d	*p*-Nitrophenyl	212	$C_{19}H_{15}N_3O_4$	65.2 (65.3	4.2 4.3	12.0 12.0)	225**	$C_{19}H_{14}N_6O_3$	60.9 (61.0	3.7 3.7	21.3 21.5)
e	*p*-Chlorophenyl	198	$C_{19}H_{15}N_2O_2Cl$	75.0 (75.2	4.9 5.0	9.2 9.2)	162‡	$C_{19}H_{14}N_5OCl$	62.7 (62.8	3.8 3.9	19.1 19.3)
f	*o*-Chlorophenyl*	—	—	—	—	—	115‡	$C_{19}H_{14}N_5OCl$	62.7 (62.8	3.8 3.9	19.3 19.3)
g	*p*-Methoxyphenyl	176	$C_{20}H_{18}N_2O_3$	71.7 (71.9	5.4 5.4	8.4 8.4)	165**	$C_{20}H_{17}N_5O_2$	66.5 (66.9	4.6 4.7	19.4 19.5)

*Compounds **4a**, **4c** and **4f** are reported in literature[7].
†PMR (**6a**): δ 2.2 (*s*, 3H, CH_3), 6.5-7.1 (*dd*, 2H, $-CH=CH-$, $J=15$ Hz), 7.1-7.8 (*m*, 10H, Ar−*H*).
PMR (**6b**): δ 2.0 (*s*, 3H, CH_3), 2.4 (*s*, 3H, $CH_3.C_6H_4$), 6.6-7.2 (*dd*, 2H, $-CH=CH-$, $J=15$ Hz), 7.0-7.8 (*m*, 9H, Ar−*H*).
PMR (**6e**): δ 2.1 (*s*, 3H, CH_3), 6.6-7.2 (*dd*, 2H, $-CH=CH-$, $J=15$ Hz), 7.2-7.9 (*m*, 9H, Ar−*H*).
‡Recrystallized from pet. ether and benzene.
**Recrystallized from benzene and ethyl acetate.

protons would have appeared as two separate doublets[1]. The IR spectra of the tetrazoles exhibited no bands due to carbonyl (1690 cm^{-1}) and azide functions ($\approx$2140 cm^{-1}).

Likewise, 3-amino-5-methylisoxazole was subjected to a similar synthetic sequence of N-acylation, chlorination and azidolysis which resulted in the formation of 5-aryl-1-(5-methyl-3-isoxazolyl)tetrazoles (**9**; Table 2).

The PMR spectrum of **9a** (Ar = phenyl) was unusual. It displayed two pairs of doublets, one at δ 2.5 and 2.6 and the other at 6.5 and 6.9 which were assignable to the methyl protons and the hydrogen of isoxazole ring, respectively. These two types of protons appeared as doublets ($J=2$ Hz) because of allylic coupling between them. To understand and explain these PMR data, the model of **9a** was examined. The molecular model showed two preferred conformations. In these conformations the phenyl and tetrazole rings are coplanar and the isoxazole is at right angles. The duplication in the methyl and the lone hydrogen resonances indicated slow rotation of the isoxazole moiety about the C – N bond on the PMR time scale. The slow rate process could be attributed to the Van der Waals interactions between the phenyl and isoxazole rings. In one conformation the lone pairs of isoxazole ring nitrogen and N-1 of the tetrazole are *syn*. In this arrangement the methyl protons and the lone hydrogen on isoxazole fall in the shielding and deshielding zones of benzene ring (due to ring current) respectively. The upfield signal (δ 2.5) out of the two doublets due to methyl protons and the downfield peak (δ 6.9) out of the two doublets due to isoxazole hydrogen belong to this conformation (Fig. 1, conformation-*A*). In the other conformation (Fig. 2, conformation-*B*) in which the isoxazole hydrogen is *syn* to the tetrazole N-1 nitrogen, neither the methyl protons are in the shielding zone nor is the isoxazole hydrogen in the deshielding zone. Therefore, the downfield signal (δ 2.6) in the pair of doublets assigned

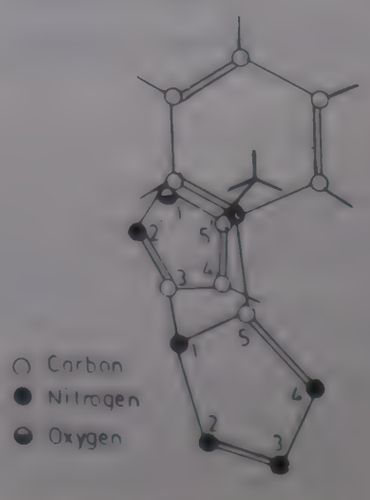


FIG. 1 Conformation - A

Table 2 -Physical and Analytical Data of 3-Acylaminoisoxazoles (**8**) and 5-Aryl-1-(3-methyl-4-isoxazolyl)tetrazoles (**9**)

Compd	Ar	3-Acylaminoisoxazoles (**8**)					Isoxazolyltetrazoles (**9**)*				
		m.p. °C	Mol. formula	Found (%) (Calc.)			m.p. °C	Mol. formula	Found (%) (Calc.)		
				C	H	N			C	H	N
a	Phenyl	153	$C_{11}H_{10}N_2O_2$	65.3	4.9	13.8	98†	$C_{11}H_9N_5O$	58.1	4.0	30.8
				(65.3	5.0	13.9)			(58.1	4.0	30.8)
b	*p*-Chlorophenyl	205	$C_{11}H_9N_2O_2Cl$	55.9	3.8	11.8	143‡	$C_{11}H_8N_5OCl$	50.6	3.1	26.8
				(55.9	3.8	11.9)			(50.6	3.1	26.8)
c	*o*-Chlorophenyl	105	$C_{11}H_9N_2O_2Cl$	55.9	3.8	11.9	142‡	$C_{11}H_8N_5OCl$	50.5	3.0	26.8
				(55.9	3.8	11.9)			(50.6	3.1	26.8)
d	*p*-Tolyl	191	$C_{12}H_{12}N_2O_2$	66.6	5.5	12.9	125†	$C_{12}H_{11}N_5O$	42.1	3.2	20.5
				(66.7	5.6	13.0)			(42.2	3.3	20.5)
e	*p*-Methoxyphenyl	173	$C_{12}H_{12}N_2O_3$	62.0	5.1	12.1	168‡	$C_{12}H_{11}N_5O_2$	56.0	4.3	27.2
				(62.1	5.2	12.1)			(56.0	4.3	27.2)
f	*p*-Nitrophenyl	175	$C_{11}H_9N_3O_4$	53.4	3.6	17.0	260**	$C_{11}H_8N_6O_3$	48.5	2.9	25.7
				(53.4	3.6	17.0)			(48.5	2.9	25.7)

*PMR (**9a**): δ 2.5, 2.6 (*d*, 3H, isoxazole CH_3, J_{AB}=2 Hz), 6.5, 6.9 (*d*, 1H, isoxazole H-4, J_{AB}=2 Hz), 7.3-8.2 (*m*, 5H, Ar–*H*).
PMR (**9c**): δ 2.4, 2.5 (*d*, 3H, isoxazole CH_3, J_{AB}=2 Hz), 6.4, 6.8 (*d*, 1H, isoxazole H-4, J_{AB}=2 Hz), 7.0-8.0 (*m*, 4H, Ar–*H*).
PMR (**9e**): δ 2.5, 2.6 (*d*, 3H, isoxazole CH_3, J_{AB}=2 Hz), 6.5, 6.9 (*d*, 1H, isoxazole H-4, J_{AB}=2 Hz), 3.8 (*s*, 3H, $CH_3O.C_6H_4$), 7.2-7.9 (*m*, 4H, Ar–*H*).
†Recrystallized from aq. ethanol.
‡Recrystallized from pet. ether and benzene.
**Recrystallized from acetone.

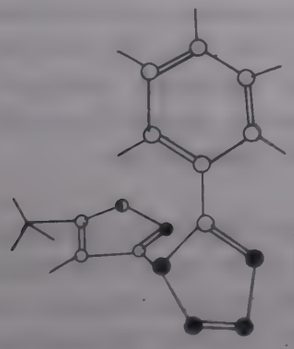


FIG. 2 Conformation - B

to the methyl protons and the upfield peak (δ 6.5) in the pair of doublets due to isoxazole hydrogen belong to this steric arrangement. Of the two conformations, *A* is less stable because of the repulsive interactions between lone pairs on the two *syn*-nitrogens. This is evident from the sizes of upfield doublet (at δ 2.5) and downfield doublet (at δ 6.9) which are smaller than their companions, viz. signals at δ 2.6 and 6.5, the ratios being 3:4. This type of study on the existence of preferred conformations (in the molecules with restricted rotation) with the help of PMR data has earlier been reported[10].

The mass spectrum of 1-(3-methyl-5-styryl-4-isoxazolyl)-5-(*p*-tolyl)tetrazole (**6b**) showed fragmentations diagnostic of both the heterocycles. The base peak at *m/z* 131 was due to the cinnamoyl cation formed as a result of the cleavage of the N–O bond, the weakest linkage of isoxazole[11,1], followed by skeletal rearrangement (Chart 1). The intense peak appearing at *m/z* 315 was due to the isoxazolyldiazirine ion formed by the expulsion of nitrogen molecule from the tetrazole moiety of M^+ (*m/z* 343). The formation of diazirine was confirmed by a peak at *m/z* 132 assignable to the aryldiazirine cation. The mass spectrum of 1-(5-methyl-3-isoxazolyl)-5-phenyltetrazole (**9a**), also showed the fragmentation pattern typical of isoxazole (acetyl cation at *m/z* 43) and tetrazole (loss of a nitrogen molecule from M^+ leading to a peak at *m/z* 199) ring systems. The base peak at *m/z* 105 is presumably due to benzazirine formed by the cleavage of tetrazole ring and the transfer of two hydrogens from the isoxazole moiety (Chart 1). The isomeric aldimine cation which is not that stable as the benzazirine, may not give rise to the base peak.

Pyrolysis of the products **6** and **9** is underway.

Experimental Procedure

All melting points are uncorrected. Purity of the compounds was checked by TLC. The IR spectra were run in KBr on a Perkin-Elmer 283 spectrophotometer (ν_{max} in cm^{-1}), 90 MHz PMR spectra in $CDCl_3$ on a Varian EM-390 spectrometer using TMS as the internal reference (chemical shifts in δ, ppm) and the mass spectra on a Varian MAT CH-7 instrument at 70 eV.

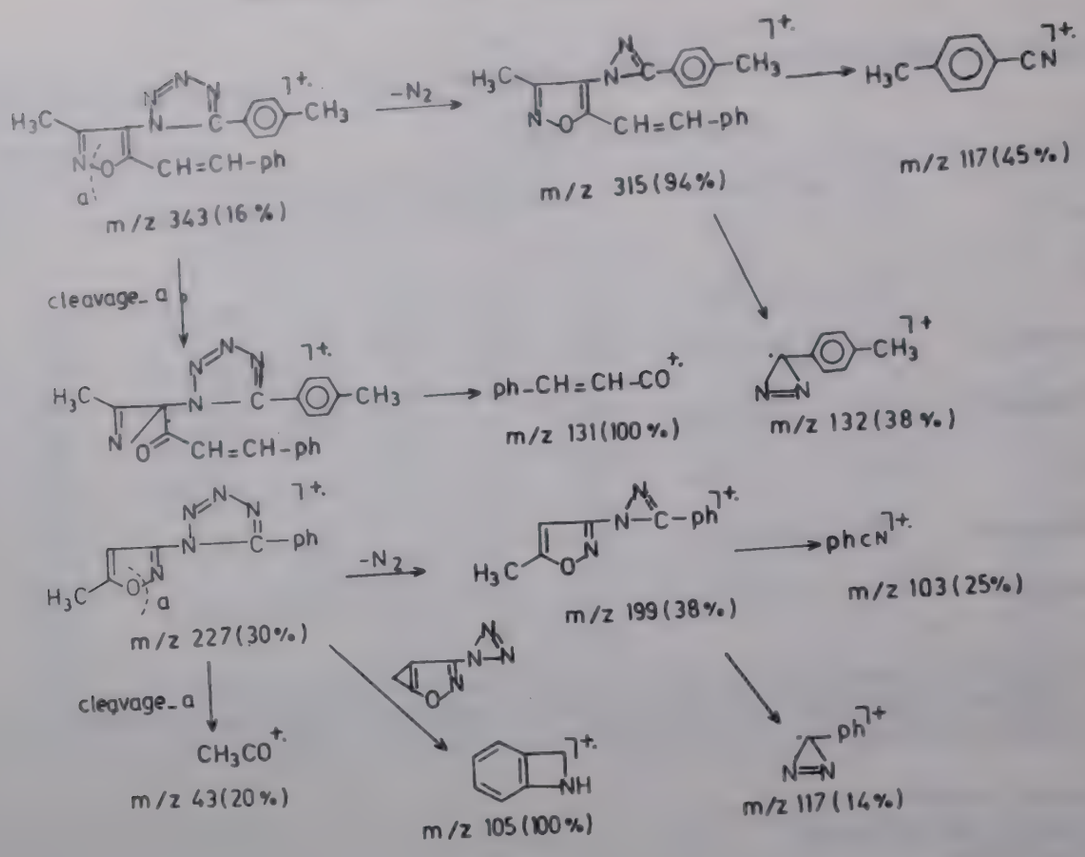


Chart 1

4-Aroylamino-3-methyl-5-styrylisoxazoles (**4**; *Table* 1)

To 4-amino-3-methyl-5-styrylisoxazole[7] (0.01 mol) in dry benzene (50 ml), was added an equimolar proportion of an acid chloride dropwise at room temperature with stirring. The reaction was carried for 15-30 min, cooled and the separated product filtered and recrystallized from aq. ethanol; IR: 3250 (amide NH), 1680 (amide C=O).

5-Aryl-1-(3-methyl-5-styryl-4-isoxazolyl)-tetrazoles (**6**; *Table* 1)

A mixture of **4** (0.01 mol) and PCl_5 (0.01 mol) was heated in an oil-bath at 120° for 2 hr. After the evolution of hydrogen chloride had ceased, traces of $POCl_3$ were removed under reduced pressure. The imidoyl chloride thus obtained, was treated with excess of a cold solution of sodium azide and sodium acetate in aq. acetone and the reaction mixture stirred overnight. The solid that separated was filtered and recrystallized from an appropriate solvent. In some cases, where the solid did not separate, the reaction mixture was extracted with ether and evaporated at ambient temperature. The gummy material thus obtained was triturated with pet. ether repeatedly and treated with benzene to give a solid which was recrystallized from a suitable solvent (Table 1).

3-Aroylamino-5-methylisoxazoles (**8**)

3-Amino-5-methylisoxazole (0.01 mol) was treated with appropriate aromatic acid chlorides (0.01 mol) in dry benzene for 15-30 min. The reaction mixture was cooled and the separated product filtered and recrystallized from aq. ethanol to get **8** (Table 2); IR: 3200 (amide NH), 1690 (amide C=O).

5-Aryl-1-(5-methyl-3-isoxazolyl)tetrazoles (**9**)

Compounds **8** (0.01 mol) were reacted with PCl_5 (0.01 mol) and the reaction mixture in each case was heated at 115° for 2 hr. After the removal of $POCl_3$, the imidoyl chloride obtained was subjected to azidolysis by treatment with a cold solution of sodium azide and sodium acetate in aq. acetone. The solid that separated after overnight stirring was recrystallized from a suitable solvent to get **9** (Table 2).

Acknowledgement

The authors thank Prof. E V Sundaram, Head, Department of Chemistry, Kakatiya University for facilities. One of them (B P) is grateful to CSIR, New Delhi for the award of a junior research fellowship.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1214-1215

Synthesis of (+)-*ar*-Turmerone Employing Organolithium Reagents†

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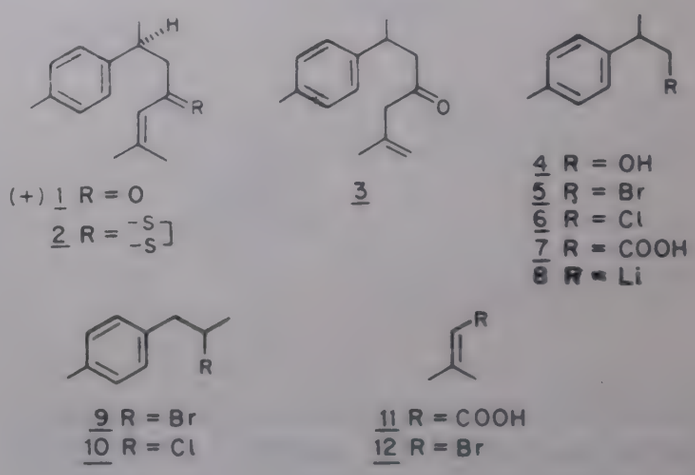
Received 19 *May* 1986; *accepted* 30 *June* 1986

Chlorodecarboxylation of (±)-β,4-dimethylbenzenepropionic acid (**7**) with lead tetraacetate and lithium chloride furnishes (±)-1-(2-chloro-1-methylethyl)-4-methylbenzene (**6**). Lithium salt of 3-methyl-2-butenoic acid (**11**) reacts with 2-(*p*-tolyl)-*n*-propyllithium (**8**) prepared *in situ* from (±)-**6** to furnish (±)-*ar*-turmerone (**1**). Optically active (+)-**1** is prepared by reacting lithium salt of the acid (+)-**7** with isobutenyllithium.

There are several reports[1a-c] on the synthesis of *ar*-turmerone (**1**), the major component of the essential oil prepared from the rhizomes of *Curcuma longa* Linn. Determination of the absolute configuration of (+)-**1** and synthesis of some related ketones have been reported from this laboratory[2,3]. We describe in this paper the synthesis of **1** employing two different routes.

In some of the syntheses reported, **1** is not obtained directly[4]; instead it is prepared by isomerising the ketone (**3**). In the present approach **1** is obtained, free from isomer (**3**), in high yields using intermediates (**11**) and (**12**) which determine the location of the double bond. The synthesis proceeding via the dithioacetal[5,6] (**2**) is comparatively good but suffers from the drawback that in the final deblocking step the yield is only 60%. Though there are several reports on the synthesis of **1** only a few of them[7-14a] deal with optically active product. The ready availability of optically active acid[7], (+)-**7** prompted us to employ it in the synthesis of (+)-**1**; since the chiral centre is not adjacent to carbonyl group in (+)-**7**, it is a good intermediate for the synthesis of (+)-**1**. Ketones can be prepared in excellent yields employing organolithium reagents. It appeared attractive to use this approach for the synthesis of **1**.

The primary alcohol (**4**) was prepared through hydroboration of the 1-methyl-4-(1-methylethenyl)-benzene. The preparation of the bromide (**5**) by reacting the alcohol (**4**) with HBr has been reported in literature[8]; however, in our hands the product of the reaction was a 9:1 mixture (PMR) of the bromides (**9**) and (**5**) respectively. There are precedents in literature[9] for this type of rearrangement. The reaction of **4** with PBr_3 also furnished a 7:3 mixture of bromides (**9** and **5**). The reaction of **4** with thionyl chloride furnished a 2:3 mixture (PMR) of chlorides (**6** and **10**). While the



above reactions furnished a mixture of halides and hence were not of preparative value, the chlorodecarboxylation of the acid (**7**) furnished the primary chloride (**6**) free from the secondary isomer (**10**). When a mixture of (±)-**6**, lithium salt of the acid (**11**) and lithium in dry ether was stirred (±)-**1** was obtained in good yield. In the second approach a mixture of lithium salt of acid (+)-**7**, bromo compound (**12**) and lithium in dry ether was stirred to furnish (+)-**1**. The optical purity of the synthetic (+)-**1** was the same as that of the starting (+)-**7**.

Experimental Procedure

All m.ps. and b.ps (bath temp) are uncorrected. IR spectra was recorded on a Perkin-Elmer infracord 137 spectrophotometer (ν_{max} in cm^{-1}) and PMR spectra on a Varian T-60 spectrometer using TMS as internal standard (chemical shift in δ-scale). Optical rotations were taken on a Perkin-Elmer-140 polarimeter.

1-*Methyl*-4-(1-*methylethenyl*)*benzene*

A mixture of α,α,4-trimethylbenzenemethanol[10] (1.3 g) and $KHSO_4$ (20 mg) was heated at 100-200°/100 mm. The distillate obtained was extracted with ether (2 × 10 ml), the ether extract washed with water,

brine and dried (Na_2SO_4). The solvent was evaporated and the residue was distilled at 100° (bath)/100 mm to give the desired product; yield 1.2 g (98%) (lit.[11] b.p. 184-85°).

β,4-*Dimethylbenzeneethanol* (**4**)

Boron trifluoride etherate (1.4 ml) was added to a mixture of 1-methyl-4-(1-methylethenyl)benzene (3.96 g) and $NaBH_4$ (0.31 g) in dry tetrahydrofuran (20 ml) at 25°. After 2 hr water (2 ml) was added slowly followed by 3*M* NaOH (3.3 ml) and subsequently 30% H_2O_2 (3.3 ml). After stirring the above mixture for 1 hr NaCl (5 g) was added and filtered. Evaporation of the solvent from the filtrate and distillation of the residue under reduced pressure gave **4**; yield 4.32 g (96%); b.p. 100° (bath)/6 mm. (lit.[8] b.p. 102°/5 mm).

Reaction of $SOCl_2$ with **4**

A mixture of **4** (3.6 g) and $SOCl_2$ (15 ml) was heated under reflux for 3 hr. Excess $SOCl_2$ was removed under reduced pressure and the residue distilled at 90°/6 mm to give (3.65 g), 7:3 mixture of **10** and **6** as revealed by PMR.

(±)-1-(2-*Chloro*-1-*methylethyl*)-4-*methylbenzene* (**6**)

A mixture of (±)-**7**[12] (1.78 g), lithium chloride (0.42 g), dry benzene (70 ml) and $Pb(OAc)_4$ (4.43 g), was stirred at 25° for 1 hr in the dark, followed by heating under reflux for 5 hr. The reaction mixture was cooled to 25°, treated with ethanediol (5 ml) to destroy the excess of $Pb(OAc)_4$, poured into water at 0° and extracted with ether (3 × 30 ml). The ether extract was washed with 10% aq $NaHCO_3$ [the $NaHCO_3$ layer was acidified with dil. HCl and extracted with ether to furnish the unreacted starting (±)-**7** (1.2 g)], water, brine and dried (Na_2SO_4). The solvent was evaporated and the residue distilled at 90°/6 mm to give halide (±)-**6**, yield 0.412 g (75%) (based on the recovery of the starting acid); PMR: 1.33 (*d*, 3H, *J* = 7 Hz, CH_3-CH), 2.3 (*s*, 3H, CH_3-Ar), 2.96 (*sextet*, *J* = 7 Hz, $-CH-$), 3.33 (*m*, 2H, CH_2Cl), 7.03 (*m*, 4H, Ar−H) (Found: C, 71.2; H, 7.2. $C_{10}H_{13}Cl$ requires C, 71.4; H, 7.6%).

2-*Methyl*-6-(4-*methylphenyl*)-2-*heptene*-4-*one* [(+)-**1**]

The halide (**12**) (2.79 g) in dry ether (5 ml) was added to a mixture of lithium salt (1.84 g), prepared from the acid (+)-**7** {$[\alpha]_D^{25} = +45.5°$; $C = 5$, C_6H_6; e.e. 70% lit.[4a] $[\alpha]_D = +65°$, $C = 4.6$ C_6H_6}, lithium (0.28 g) and dry ether (10 ml) under N_2 atmosphere. After 24 hr the reaction mixture was cooled to −10° and added gradually to a mixture of ice, NH_4Cl and ether with stirring. The aqueous layer was extracted with ether (2 × 10 ml) and the combined ether extract washed with water, 10% aq. $NaHCO_3$, brine and dried (Na_2SO_4). The solvent was evaporated and the residue distilled at 160°/10 mm to give the product (+)-**1**; yield 1.57 g, (69.9%) {$[\alpha]_D^{25} = +40°$, $C = 5$, $n-C_6H_{14}$, e.e 72%, lit.[7] $[\alpha]_D^{22} = +64°$; $C = 4.5$, $n-C_6H_{14}$}. The product was fully characterised by comparing GLC, IR and PMR with an authentic sample.

2-*Methyl*-6-(4-*methylphenyl*)-2-*heptene*-4-*one* [(±)-**1**]

(±)-**6** (1.68 g) was added to a mixture of lithium salt of the acid (**11**), (1.06 g) lithium (0.28 g) and dry ether (10 ml) at 25°C under N_2 atmosphere. After 24 hr the reaction mixture was worked-up as above to give (±)-**1**; yield 1.2 g (55%).

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1216-1219

Plant Growth Regulators: Syntheses of *n*-Triacontynol, *n*-Triacontenol & *n*-Triacontanol

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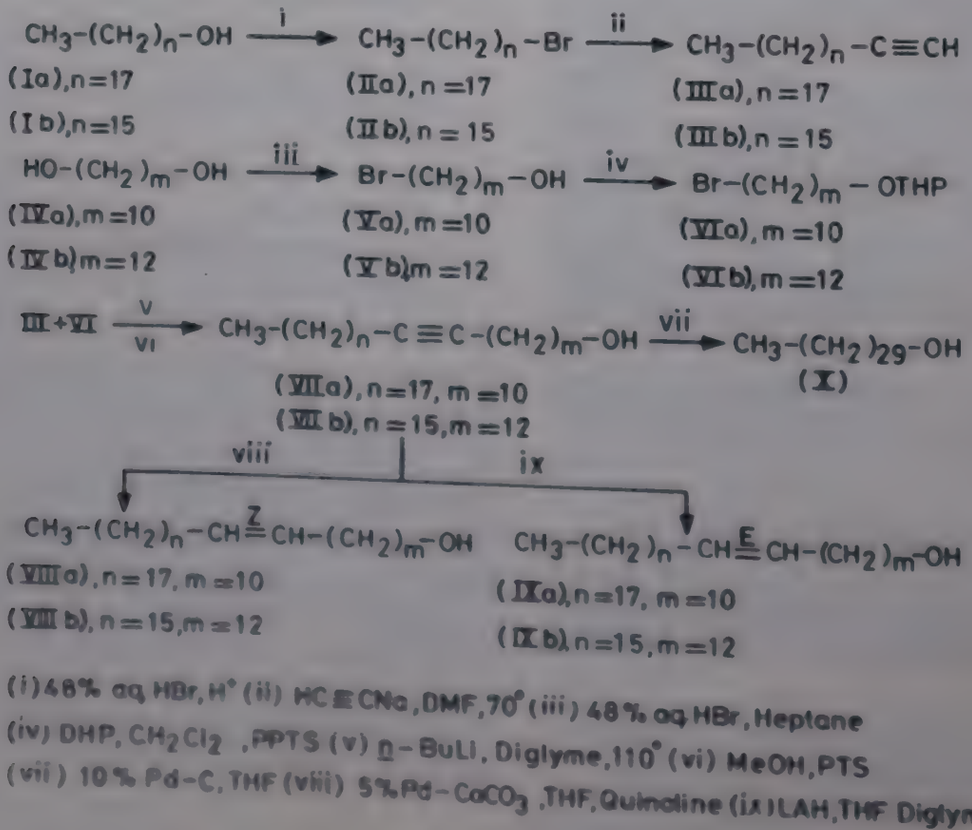
Received 27 *February* 1986; *accepted* 27 *May* 1986

Convenient syntheses of *n*-triacontynols (VII), *n*-triacontenols (VIII and IX) and *n*-triacontanol (X) are described. The alkynes (III) are coupled with bromo THP-ethers (VI) to yield the disubstituted *n*-triacontynols (VII). These on selective partial hydrogenation afford the disubstituted *n*-triacontenols (VIII and IX). Alkynols (VII) on complete hydrogenation give the *n*-triacontanol (X). Biological studies reveal that the acetylenes (VII) and olefins (VIII and IX) are better plant growth regulators than the *n*-triacontanol (X).

The synthesis of *n*-triacontanol, a naturally occurring plant growth regulator (PGR), has been recently reported[1] from our laboratory. Herein we wish to report a general and practical synthesis of *n*-triacontanol, by an alternate route. The present synthetic approach (Scheme 1) offers additional advantages, as it also provides the disubstituted acetylenes and olefins of *n*-triacontanol for PGR studies.

Bromides (IIa and IIb) prepared by standard procedures on treatment with sodium acetylide in DMF[2] provided the corresponding alkynes (IIIa and IIIb). Partial bromination[3] of the diols (IVa and IVb) in a biphase reaction using 48% aq. HBr in heptane under reflux yielded the corresponding bromohydrins (Va and Vb). The hydroxy groups in Va and Vb were protected as THP ethers[4] to furnish the corresponding bromopyranyl ethers (VIa and VIb). In the key step of carbon-carbon coupling, the alkynes (IIIa and IIIb) were metalated with *n*-BuLi in diglyme[5] and then treated with the bromides (VIa and VIb) respectively and the resulting coupled products on depyranylation with PTS/methanol afforded the corresponding *n*-triacontynols (VIIa and VIIb). Partial hydrogenation of VIIa and VIIb using Lindlar's catalyst in THF



SCHEME 1

Table 1—Effect of C_{30}-Alcohol Analogues On Root and Shoot Growth in Hypocotyl Cuttings of Bean (*Phaseolus vulgaris* Linn.)

C_{30}-Alcohol analogue	Fresh Weight (gms)			
	Root		Shoot	
	2.5 ppm	5 ppm	2.5 ppm	5 ppm
	*Excised seedlings**			
Distilled water	0.827	0.669	2.454	2.242
X	0.956	0.701	2.625	2.487
VIIa	1.308	1.040	2.801	2.213
VIIIa	1.068	0.753	2.876	2.472
IXa	1.268	0.920	3.080	1.556
	*Intact seedlings**			
Distilled water	0.734	0.966	2.662	3.371
X	0.810	0.425	2.348	1.609
VIIa	0.910	1.12	2.479	2.594
VIIIa	1.115	1.274	2.870	2.908
IXa	1.075	0.597	3.031	1.715

*7 days old and treated for 7 days.

afforded the corresponding *cis-n*-triacontenols (VIIIa and VIIIb). VIIa and VIIb when heated with LAH in diglyme[6] resulted in *trans-n*-triacontenols (IXa and IXb), respectively. Complete hydrogenation of VII over 10% Pd/C catalyst yielded the desired *n*-triacontanol (X). The physical properties of X are in good agreement with those reported for *n*-triacontanol.

The PGR studies of VIIa, VIIIa, IXa and X revealed that *n*-triacontynol (VIIa) and *n*-triacontenols (VIIIa and IXa) have better activity than the naturally occurring *n*-triacontanol (X) at 2.5 ppm concentration but inhibition of root formation is observed at 5 ppm concentration (Table 1). The biological results on structure-PGR activity relationship will be published elsewhere.

Experimental Procedure

Melting points reported are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer model 783 spectrophotometer and PMR spectra on a Varian A60A instrument in $CDCl_3$ solution containing TMS as an internal standard (chemical shifts in δ, ppm). Mass spectra were recorded on a VG Micromass 7070 F instrument.

The reactions involving organometallic reagents were conducted under argon atmosphere and the solvents/reagents were transferred with the help of syringes. The anhydrous solvents were either freshly prepared prior to use, or were stored over molecular sieves (type 4A).

n-Eicosyne (IIIa) and octadecyne (IIIb)

Anhydrous ammonia (100 ml) was collected in a flask equipped with a gas inlet tube, a cold finger condenser (for dry ice-acetone mixture) and a dropping funnel. To this ferric nitrate (0.2 g) was added. Sodium (3 g, 0.13 g atom) was introduced in the form of small pieces during 30 min, and the stirring was continued till the blue colour disappeared and a grey suspension was formed. Acetylene gas was then slowly introduced into the flask till all the precipitate (due to sodaamide) dissolved forming a black solution. Thereafter ammonia was slowly allowed to evaporate and stearyl bromide (20 g, 0.06 mol) in dry dimethylformamide (30 ml) was added during 30 min. The flask was immersed in an oil-bath, and slowly heated to 70°. After 4 hr of stirring at 70°, the reaction mixture was cooled and quenched by adding a saturated solution of ammonium chloride. The mixture was diluted with water (200 ml) and extracted with ether (4 × 75 ml). The combined ether extract was washed with water, brine and dried (Na_2SO_4). Removal of solvent followed by distillation of the residue under reduced pressure afforded the pure *n*-eicosyne (IIIA); yield 11.7 g (70%), b.p. 170-76°/8 mm (lit.[7]/132-40°/2 mm); IR: 3300, 2920, 2850, 2100 and 1470; PMR: 0.89 (*br*, 3H, $-CH_3$), 1.25 (*bs*, 32H, 16 × $-CH_2-$), 1.9 (*m*, 1H, $-C\equiv CH$), 2.2 (*br*, 2H, $CH_2-C\equiv CH$). Likewise, *n*-octadecyne (IIIb) was prepared from the bromide (IIb) (18.3 g, 0.06 mol) and sodium (3 g, 0.13 g atom); yield 9.8 g (65%); b.p. 140°/1 mm (lit.[8] 180°/15 mm).

10-*Bromodecan*-1-*ol* (*Va*) *and* 12-*bromododecan*-1-*ol* (*Vb*)

A mixture of decanediol (8.7 g, 0.05 mol), heptane (50 ml) and 48% aq. HBr (20 ml) was stirred under reflux for 25 hr. The organic layer was separated and the aqueous layer extracted with ether (3 × 50 ml). The combined organic extract was washed with water, 5% aq. sodium carbonate, brine and dried (Na_2SO_4). Removal of solvent followed by chromatography of the resulting residue over silica gel column using ether in petroleum ether (0-30% gradients) for elution provided the desired bromohydrin (Va) as a thick liquid; yield 8.3 g (70%); TLC single spot (silica gel, benzene, $R_f = 0.3$); IR: 3350, 2920, 2850, 1460, 1260 and 1060; PMR: 1.33 (*s*, 16H, 8 × $-CH_2-$), 1.65 (*s*, 1H, D_2O exchangeable), 3.41, 3.65 (2*t* overlapping, 4H, $-CH_2OH$ & $-CH_2Br$).

Likewise, 12-bromododecan-1-ol (Vb) was prepared from IVb (10.1 g, 0.05 mol), heptane (50 ml) and 48% aq. HBr (20 ml), yield 9.3 g (70%).

10-Bromo-1-tetrahydropyranyloxydecane (VIa) and 12-bromo-1-tetrahydroxypyranyloxydodecane (VIb)

To a stirred and cooled (0°) solution of Va (7.1 g, 0.03 mol) in methylene chloride (30 ml), PPTS (0.5 g) and dihydropyran (2.9 g, 0.04 mol) were added. The mixture was stirred at 0° for 30 min and then at ambient temperature for 4 hr. The reaction mixture was diluted with ether, the organic layer washed with 5% aq. sodium carbonate, water, brine and dried (Na_2SO_4). Removal of solvent followed by flash column chromatography of the residue over alumina (grade II) afforded the pure VIa; yield 9.1 g (95%); IR: 2920, 2850, 1460, 1075, 1030, 910 and 870; PMR: 1.33 (*s*, 16H, $8\times-CH_2-$), 1.65 (*bs*, 6H, $3\times CH_2-$), 3.28-3.66 [*m*, 6H, $-CH_2Br$ & $(CH_2O)_2$], 4.6 (*bs*, 1H, $-OCHO-$).

Likewise, 12-bromo-1-tetrahydropyranyloxydodecane (VIb) was prepared from Vb (8 g, 0.03 mol), PPTS (0.5 g), and dihydropyran (2.9 g, 0.04 mol), yield 9.8 g (94%).

Triacont-11-yn-1-ol (VIIa) and triacont-13-yn-1-ol (VIIb)

A solution of the alkyne IIIa, (5.6 g, 0.02 mol) in dry diglyme (35 ml) was cooled to (0°) and treated with *n*-butyllithium (32 ml, 1.6 molar solution in hexane) during 15 min. The reaction mixture was stirred at ambient temperature for 2 hr and then at 50° for additional 1 hr. The bromopyranyl ether (VIa, 3.2 g, 0.01 mol) in diglyme (5 ml) was added to the above reaction and mixture was stirred at 110° for 2 hr. Usual work-up with ether as solvent gave a residue, which was treated with methanol (100 ml), *p*-toluenesulphonic acid (0.5 g) and refluxed on a water-bath for 3 hr. After removal of methanol under reduced pressure, the residue was diluted with water (300 ml), and extracted with chlororoform (3×50 ml). The combined chloroform extract was washed with water, 5% aq. sodium carbonate, brine and dried (Na_2SO_4). Removal of solvent followed by crystallisation of the residue from petroleum ether provided the alkynol (VIIa); yield 3.1 g (70%); m.p. 72-73°; IR (KBr): 3350, 2920, 2850, 1470, 1060 and 720; PMR: 0.88 (*br*, 3H, $-CH_3$), 1.28 (*bs*, 48H, $24\times-CH_2-$), 2.08 (*br*, 5H, $-CH_2-C\equiv C-CH_2-$ & $-CH_2OH$), 3.6 (*t*, 2H, $J=6$ Hz, $-CH_2OH$); MS: *m/z* 434 (M^+), 416 (M-18) (Found: C, 82.9; H, 12.6. $C_{30}H_{58}O$ requires C, 82.9; H, 13.3%).

Likewise, VIIb was prepared from the alkyne (IIIb, 5 g, 0.02 mol) in dry diglyme (35 ml), *n*-butyllithium (32 ml, 1.6 molar solution in hexane) and bromopyranyl ether (VIb) (3.5 g, 0.01 mol), yield 3.1 g (72%); m.p. 71-72°; IR and PMR data were similar to those of VIIa.

(Z)-Triacont-11-en-1-ol (VIIIa) and (Z)-triacont-13-en-1-ol (VIIIb)

To a solution of the alkynol (VIIa, 0.43 g, 1 mmol) in tetrahydrofuran (2 ml), a drop of quinoline and the catalyst (5% Pd-$CaCO_3$, 12 mg) were added and the mixture was stirred under a positive pressure of hydrogen for 4 hr. Thereafter the reaction mixture was diluted with ether and filtered through a short pad of silica gel. Removal of solvent followed by crystallisation of the residue from pet-ether provided the pure (*Z*)-alkenol (VIIIa); yield 0.39 g (90%); m.p. 52-53°; IR (KBr): 3350, 2920, 2850, 1470, 1060 and 720; PMR: 0.88 (*br*, 3H, $-CH_3$), 1.26 (*bs*, 52H, $26\times-CH_2-$), 3.67 (*t*, 2H, $J=6$ Hz, $-CH_2OH$), 5.38 (*m*, 2H, $-CH=CH-$); MS: $m/z=436$ (M^+), 418 (M-18$^+$).

Likewise, (*Z*)-alkenol (VIIIb) was prepared from VIIb. IR and PMR data were similar to those of VIIIa.

(E)-Triacont-11-en-1-ol (IXa) and (E)-triacont-13-en-1-ol (IXb)

To a slurry of lithium aluminium hydride (0.11 g, 3 mmol) and a mixture of tetrahydrofuran (1 ml) and diglyme (2 ml), was added the alcohol (VIIa, 0.43 g, 1 mmol) in one lot with stirring. The reaction mixture was placed in an oil-bath and the temperature was gradually raised to 140°. The low boiling distillate was removed, the mixture stirred under reflux for 36 hr, cooled in an ice-bath and the excess lithium aluminium hydride decomposed by the addition of a saturated solution of sodium sulphate. It was filtered and the granular white solid was thoroughly extracted with ether. Removal of solvent followed by crystallisation of the residue from hexane afforded the pure (*E*)-alkenol (IXa); yield 0.3 g (70%); m.p. 61-62°; IR (KBr): 3350, 2920, 2850, 1470, 980 and 720; PMR 0.82 (*br*, 3H, $-CH_3$), 1.2 (*bs*, 52H, $26\times-CH_2-$), 3.56 (*t*, 2H, $J=6$ Hz, $-CH_2OH$), 5.33 (*m*, 2H. $-CH=CH-$); *m/z* 436 (M^+), 418 (M-18$^+$).

Likewise, (*E*)-alkenol (IXb) was prepared from VIIb. IR and PMR data were similar to those of IXA.

n-Triacontanol (X)

To a solution of alkynol (VIIa, 0.35 g, 8 mmol) in tetrahydrofuran (5 ml), 10% Pd/C (13 mg) was added, and the mixture was stirred vigorously under a positive pressure of hydrogen for 4 hr. Usual work-up followed by crystallisation of the residue from pet. ether afforded the desired X, yield 0.3 g (95%); m.p. 86-87° (lit.[1] 86-87°; IR (KBr): 3330, 2940, 1450, 1060 and 720.

Likewise, alkynol (VIIb) also gave *n*-triacontanol. Identity of X was also established by direct comparison (TLC, m.p., IR) with authentic sample[1].

Acknowledgement

One of the authors (RRI) thanks the Department of

Atomic Energy, Bombay for the award of a research fellowship.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1220-1223

Synthesis of (4*E*, 7*Z*)-4,7-Tridecadienyl Acetate & (4*E*, 7*Z*, 10*Z*)-4,7,10-Tridecatrienyl Acetate—The Sex Pheromones of Potato Tuberworm Moth†

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Received 12 *May* 1986; *accepted* 6 *June* 1986

(4*E*, 7*Z*)-4,7-Tridecadienyl acetate (**1**) and (4*E*, 7*Z*, 10*Z*)-4,7,10-tridecatrienyl acetate (**2**), the sex pheromones of potato tuberworm moth have been synthesized from a common intermediate 1-hexen-5-yn-3-ol (**3**) employing Claisen rearrangement as the key step to generate the *trans*-double bond.

The potato tuberworm moth, *Phthorimaea operculella* is a key pest of potato in many areas of the world. Roelofs *et al.*[1] isolated the sex pheromone from the abdominal tips of female potato tuberworm moth and identified its structure as (4*E*, 7*Z*)-4,7-tridecadienyl acetate (**1**). Later Yamaoka and coworkers[2] isolated another sex pheromone from the female potato tuberworm moth and assigned its structure as (4*E*, 7*Z*, 10*Z*)-4,7,10-tridecatrienyl acetate (**2**). Recently it was found[3] that a 1:1 mixture of **1** and **2** is more attractive against potato tuberworm moth than individual pheromone.

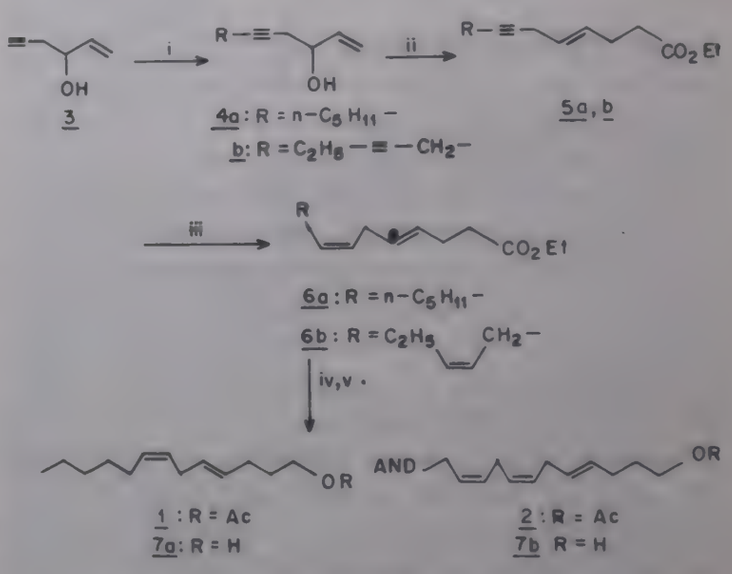
Although several syntheses of **1** were reported[4], only one or two syntheses[5] for **2** are known so far. As a part of our programme on insect sex pheromones of indigenous crops, we were interested in the synthesis of **1** and **2**. Our aim was to prepare these pheromones in gram quantities by a suitable methodology, which we wish to report in this paper.

The synthetic strategy reported here involved the use of properly functionalised intermediate, 1-hexen-5-yn-3-ol[6] (**3**), common for both **1** and **2**. The acetylenic portion in **3** has been exploited for C–C bond formation as well as a source for *cis*-double bond. While allylic alcohol portion of **3** rendered the generation of *trans*-double bond coupled with two carbon homologation via Claisen rearrangement.

Synthesis of (4*E*,7*Z*)-4,7-*tridecadienyl acetate* (**1**):

The sequence of reactions leading to **1** is shown in Scheme 1. The intermediate **3** was prepared by the modified method[6,7] from propargyl bromide and acrolein employing aluminium instead of magnesium. Compound **3** on reaction with lithium amide in liquid ammonia at $-33° \pm 3°$ produced a dianion which on treatment with 1-bromopentane afforded 1-undecen-5-yn-3-ol[7] (**4a**) in 70% yield. When **4a** and triethyl orthoacetate were heated in the presence of catalytic amount of propionic acid a Claisen rearrangement[8] occurred to afford ethyl 7-tridecyn-4(E)-enoate (**5a**) as a single (TLC, GLC) geometric isomer. This *trans* geometry was assigned on the basis of ample precedent[8]. In addition, the given structure was suggested by IR spectrum in which the presence of a strong absorption at 965 cm^{-1} (for *trans* double bond) and absence of absorption in the region of 695-735 cm^{-1} (*cis*-double bond) were revealed. Partial reduction of triple bond in **5a** over Lindlar catalyst[9] in hexane gave **6a**, which on LAH reduction in ether yielded the alcohol (**7a**). Conventional acetylation of **7a** with acetic anhydride and pyridine gave the desired **1** in an overall yield of 90% from **6a**. The synthetic **1**

SCHEME-1



i) $LiNH_2$ in Liq. NH_3, n-$C_5H_{11}Br$ or EtMgBr, $C_2H_5-\equiv-CH_2Br$
ii) $H_3CC(OEt)_3$, H_3CCH_2COOH, Δ iii) H_2, Pd-$CaCO_3$/QUINOLINE
iv) LAH-THF/ETHER v) Ac_2O, PYRIDINE

†NCL Communication No. 4016

had PMR, IR data identical with those reported for a sample of **1** synthesised by earlier workers[4].

Synthesis of (4*E*,7*z*,10*Z*)-4,7,10-*tridecatrienyl acetate* (**2**)

The synthesis of **2** was carried out in more or less the same fashion as described for **1** except for alkylation reaction (Scheme 1). Alkylation of **3** with 1-bromopent-2-yne in the presence of lithium amide in liquid ammonia could not give **4b** in satisfactory yield. However, when **3** was reacted with 2 equivalents of ethylmagnesium bromide, followed by reaction with 1-bromopent-2-yne containing catalytic amount of cuprous chloride 5,8-undecadiyn-1-en-3-ol (**4b**) was obtained in 60% yield. **4a** was converted into **2** by Claisen rearrangement, hydrogenation of acetylenic bond, LAH reduction to alcohol and acetylation in succession. Synthetic **2** was found identical in all respects with a sample of **2**, reported in literature[5].

Apart from the fact that the intermediate **3** is bifunctional for elaboration at both ends of the molecule, it also appears to be an attractive intermediate for the synthesis of a variety of unsaturated fatty acids possessing skipped diene systems. Work in this regard is being persued in our laboratory to produce them in order to understand their metabolism processes in the biological system.

Experimental Procedure

All b.ps are uncorrected. IR spectra were recorded as films on a Perkin-Elmer infracord model 683 spectrophotometer with NaCl optics. PMR spectra were recorded in $CDCl_3$ on Varian T-60 or Varian FT-80A or Bruker WH-90 spectrometer; chemical shifts are expressed in δ-scale, downfield from TMS internal reference. Mass spectra were recorded with a CEC spectrometer model 21-110B, using an ionizing voltage of 70 eV and a direct inlet system. The purity of all the products was checked by GLC which was carried out on a 5% OV-101 column (6′ × 1/8″), and using nitrogen as the carrier gas, with F/D detector at a flow rate of 30 ml/min.

1-*Hexene-5-yn-3-ol* (**3**)

To a mixture of aluminium (2.25 g, 0.083 g atoms), mercuric chloride (0.1 g) in THF (50 ml) was added 3-bromoprop-1-yne (15 g, 0.126 mol) at 5° and the reaction mixture was heated to 50° for 30 min. To this acrolein (7.48 g, 83 mmol) was added dropwise at 0° and heated at 50° for 2 hr. The reaction mixture was cooled to room temperature, poured in dil sulfuric acid and extracted with ether. The combined ether extract was washed with aq sodium bicarbonate, water, brine and dried (Na_2SO_4). Solvent was removed carefully and the residue was distilled under reduced pressure to afford pure **3** (7.26 g) in 69% yield, b.p. 75°/40 mm. (lit.[6] 49°/12 mm); IR: 3350 (OH), 3250 (H−C≡C), 2100 cm^{-1} (C≡C); PMR: 2.05 (*t*, *J* = 3 Hg, 1-H, H-6), 2.5 (*d*, *J* = 3 Hz, 2H, H-4), 3.7 (*bs*, 1H, OH, exchangeable with D_2O), 4.13-4.42 (*m*, 1H, H-3), 5.05-5.42 (*m*, 2H, H-1), 5.7-6.1 (*m*, 1H, H-2).

1-*Undecen-5-yn-3-ol* (**4a**)

To a freshly prepared suspension of lithium amide [from 1.1 g (0.157 g atom) of lithium and liquid ammonia (150 ml)] in liquid ammonia (250 ml) was added **3** (6 g, 63 mmol) in 10 min. After 2 hr 1-bromopentane (9.44 g, 63 mmol) in THF (20 ml) was added dropwise to the reaction mixture. After 0.5 hr ammonia was evaporated and the residue treated with ammonium chloride solution. Aqueous layer was extracted with ether and the combined extract dried (Na_2SO_4). The solvent was removed and the residue purified by column chromatography to afford pure **4a**[7] (7.26 g) in 70% yield; IR: 3340 cm^{-1} (OH); PMR: 0.9 (distorted *t*, 3H, CH_3), 1.25-1.48 (*m*, 6H, 3 × CH_2), 2.0-2.26 (*m*, 2H, H-7), 2.5 (*d*, *J* = 3 Hz, 2H, H-4), 4.07-4.34 (*m*, 2H, H-3 & OH), 5.0-5.5 (*m*, 2H, H-1), 5.7-6.1 (*m*, 1H, H-2); mass: *m/z* 166 (M^+), 109, 95 (100%), 57.

Ethyl (4*E*)-*Tridecen-7-ynoate* (**5a**)

A mixture of **4a** (4.78 g, 30 mmol), propionic acid (10 mmol) and triethyl orthoacetate (34.1 g, 0.21 mol) was heated[8] at 138° for 2 hr with distillative removal of ethanol. The solution was poured into ether (100 ml), the ether separated and washed with aq sodium bicarbonate, brine and dried (Na_2SO_4). The excess triethyl orthoacetate was removed under reduced pressure (50 mm Hg) and the crude was purified by column chromatography to afford pure **5a** (4.5 g) in 65% yield; IR: 1730 (carbonyl), 965 cm^{-1} (*trans* double bond); PMR: 0.9 (distorted *t*, 3H, CH_3), 1.28 (*t*, *J* = 6 Hz, 3H, OCH_2CH_3), 1.35-1.51 (*m*, 6H, 3 × CH_2), 2.04-2.22 (*m*, 2H, H-2), 2.26-2.4 (*m*, 4H, H-3 & H-9), 2.8-2.94 (*m*, 2H, H-6), 4.13 (*q*, *J* = 6 Hz, 2H, OCH_2-CH_3), 5.44-5.66 (*m*, 2H, olefinic), mass: *m/z* 236 (M^+), 191, 179 (100%), 163 (Found: C, 77.4; H, 8.6. $C_{15}H_{24}O_2$ requires C, 77.6; H, 8.7%).

Ethyl (4*E*,7*Z*)-4,7-*Tridecadienoate* (**6a**)

Compound (**5a**, 3.6 g, 15 mmol) was partially hydrogenated at atmospheric pressure over Pd-$CaCO_3$ (200 mg) in hexane (25 ml) containing one drop of quinoline. Usual work-up afforded **6a**[10] (2.9 g) in 80% yield; IR (neat): 1730 (carbonyl), 960 (*trans*-double bond), 735 cm^{-1} (*cis*-double bond); PMR: 0.85 (distorted *t*, 3H, CH_3), 1.03-1.3 (*m*, 9H, 3 × CH_2 and OCH_2CH_3), 1.8-2.04 (*m*, 2H, H-2), 2.13-2.28 (*m*, 4H, H-3 & H-9), 2.48-2.71 (*m*, 2H, H-6), 4.02 (*q*, *J* = 6 Hz, 2H, OCH_2CH_3), 5.08-5.36 (*m*, 4H, olefinic).

(4*E*,7*Z*)-4,7-*Tridecadien*-1-*ol* (**7a**)

To a cooled suspension of LAH (0.418 g, 11 mol) in ether (10 ml) was added compound **6a** (2.75 g, 11 mmol) in ether (25 ml). After 2 hr water (0.5 ml), sodium hydroxide (10%, 0.5 ml) and water (1.5 ml) were added in succession. Ether was separated, washed with brine and dried (Na_2SO_4). The solvent was removed to afford pure **7a**[4] (2.25 g) in 98% yield; IR: 3320 (OH), 965 (*trans*-double bond), 730 cm^{-1} (*cis*-double bond). PMR: 0.95 (distorted *t*, 3H, CH_3), 1.1-1.54 (*m*, 8H, 4 × CH_2), 1.62-1.84 (*m*, 4H, H-3 & H-9), 2.1 (*bs*, 1H, OH, D_2O exchangeable), 2.5-2.9 (*m*, 2H, H-6), 3.65 (*t*, *J* = 6 Hz, 2H, H-1), 5.2-5.5 (*m*, 4H, olefinic).

(4*E*,7*Z*)-4,7-*Tridecadienyl acetate* (**1**)

A mixture containing **7a** (1.96 g, 10 mmol), pyridine (2 ml) and acetic anhydride (2 ml) was stirred at room temperature during 12 hr. Usual work-up afforded **1** (2.142 g) in 90% yield; b.p. 112°/1 mm (lit.[4] 93°/0.05 mm); IR (neat): 1745 (carbonyl), 960 (*trans*-double bond), 735 cm^{-1} (*cis*-double bond); PMR: 0.9 (distorted *t*, 3H, CH_3), 1.12-1.64 (*m*, 8H, 4 × CH_2), 1.8-2.1 (*m*, 7H, H-3, H-9 & $-COCH_3$), 2.58-2:80 (*m*, 2H, H-6), 4.0 (*t*, *J* = 6 Hz, 2H, H-1), 5.24-5.83 (*m*, 4H, olefinic). Mass: 238 (M^+), 180, 152, 125, 96, 88. Anal. calcd. for $C_{15}H_{26}O_2$: C, 75.63; H, 10.92. Found: C, 75.47; H, 10.89%.

5,8-*Undecadiyn*-1-*en*-3-*ol* (**4b**)

To a freshly prepared ethylmagnesium bromide (90 mmol) in THF was added 1-hexen-5-yn-3-ol (**3**, 4.2 g, 45 mmol) in THF (25 ml) at room temperature. After stirring for 0.5 hr cuprous chloride (catalytic amount) was added and stirred for another 0.5 hr. To the yellow coloured solution 1-bromopent-2-yne (2.2 g, 15 mmol) in THF (10 ml) was added dropwise at room temperature, stirred at 50° for 8 hr, cooled to 0° and the reaction mixture treated with saturated ammonium chloride solution. Aqueous layer was extracted with ether. The combined ether extract was dried (Na_2SO_4), solvent removed and the residue purified by column chromatography to obtain **4b** (1.45 g) in 60% yield (based on 1-bromopent-2-yne); IR (neat): 3400 (OH), 2080 cm^{-1} (C≡C); PMR: 1.08 (*t*, *J* = 6 Hz, 3H, CH_3), 1.96-2.16 (*m*, 2H, H-10), 2.28-2.52 (*m*, 2H, H-4), 3-3.6 (*m*, 2H, H-7), 3.04 (*bs*, 1H, D_2O exchangeable), 4.04-4.36 (*m*, 1H, H-3); 5.0-5.44 (*m*, 2H, H-1), 5.68-6.08 (*m*, 1H, H-2).

Ethyl 7,10-*tridecadiyn*-4(*E*)-*enoate* (**5b**)

A solution of **4b** (1 g, 6 mmol), propionic acid (1 mmol) and triethyl orthoacetate (6.9 g, 41 mmol) was heated[8] at 138° for 2 hr with distillative removal of ethanol. The solution was poured into ether (100 ml) and the organic layer washed with aq sodium bicarbonate, water, brine and dried (Na_2SO_4). Solvent was removed and the excess triethyl orthoacetate was removed at 50 mm Hg. The residue was purified by column chromatography to afford **5b** (0.88 g) in 63% yield; IR: 1740 (carbonyl) 960 cm^{-1} (*trans* double bond); PMR: 1.1 (distorted *t*, 3H, CH_3), 1.24-1.48 (*m*, 4H, 1 × CH_2 and CH_2 CH_3), 1.3 (*t*, *J* = 6 Hz, 3H, OCH_2-CH_3), 2.36-2.52 (*m*, 2H, H-2), 2.76-2.96 (*m*, 2H, H-6), 3-3.2 (*m*, 2H, H-9), 4.08 (*q*, *J* = 6 Hz, 2H, OCH_2 CH_3), 5.36-5.72 (*m*, 2H, olefinic); mass: 232 (M^+), 129, 115, 91 (100%) (Found: C, 77.4; H, 8.5. $C_{15}H_{20}O_2$ requires C, 77.6; H, 8.6%).

Ethyl (4*E*,7*Z*,10*Z*)-4,7,10-*tridecatrienoate* (**6b**)

Compound (**5b**, 0.5 g, 2 mmol) was partially hydrogenated at atmospheric pressure over Lindlar[9] catalyst (100 mg) in hexane (8 ml) containing one drop of quinoline at atmospheric pressure. Usual work-up afforded **6b** (0.43 g) in 86% yield; IR: 1745 (carbonyl), 980 (*trans*-double bond), 760 cm^{-1} (*cis*-double bond); PMR: 0.96 (distorted *t*, 3H, CH_3), 1.32 (*t*, *J* = 6 Hz, 3H, OCH_2 CH_3), 1.88-2.12 (*m*, 4H, H-3 & H-12), 2.16-2.41 (*m*, 2H, H-2), 2.52-2.88 (*m*, 4H, H-6 & H-9), 4.08 (*q*, *J* = 6 Hz, 2H, OCH_2 CH_3), 5.12-5.6 (*m*, 6H, olefinic); mass: 236 (M^+).

(4*E*,7*Z*,10*Z*)-4,7,10-*tridecatrien*-1-*ol* (**7b**)

To a cooled suspension of LAH (50 mg, 1 mmol) in THF was added **6b** (300 mg, 1.2 mmol) in THF (2 ml). After 1 hr the reaction mixture was treated with water (0.5 ml), of 10% aq NaOH (0.5 ml) and water (1.5 ml) and extracted with ether. The combined organic layer was washed with brine, dried (Na_2SO_4) and solvent removed to afford **7b** (218 mg) in 91% yield; IR: 3480 (OH), 955 (*trans*-double bond), 770 cm^{-1} (*cis*-double bond); PMR: 0.9 (distorted *t*, 3H, CH_3), 1.24-1.96 (*m*, 2H, H-2), 2.0-2.36 (*m*, 4H, H-3 & H-12), 2.72-2.9 (*m*, 4H, H-6 & H-9), 3.7 (*t*, 2H, H-1), 5.16-5.72 (*m*, 6H, olefinic).

(4*E*,7*Z*,10*Z*)-4,7,10-*tridecatrienyl acetate* (**2**)

A mixture of **7b** (120 mg, 0.6 mmol), pyridine (0.5 ml) and acetic anhydride (0.5 ml) was stirred at room temperature during 12 hr. Usual work-up and purification of the crude through column chromatography afforded **2** (125 mg) in 90% yield; IR (neat): 1745 (carbonyl), 965 (*trans*-double bond), 760 cm^{-1} (*cis*-double bond); PMR: 0.85 (*t*, *J* = 6 Hz, 3H, CH_3), 1.44-1.68 (*m*, 2H, H-2), 1.72-2.0 (*m*, 4H, H-3 & H-12), 2.08 (*s*, 3H, $OCOCH_3$), 2.51-2.8 (*m*, 4H, H-6 & H-9), 3.9 (*t*, *J* = 6 Hz, 2H, H-1), 5.12-5.44 (*m*, 6H, olefinic) (Found: C, 76.1; H, 10.1. $C_{15}H_{24}O_2$ requires C, 76.3; H, 10.6%).

Acknowledgement

We are thankful to Dr A V Rama Rao for his helpful discussions.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1224-1227

Stereochemical Applications of Mass Spectrometry: Chemical Ionization Mass Spectra of 11-Substituted 14-Methoxy-14-azadispiro-[5.1.5.2]pentadec-9-ene-7,15-diones & Related Compounds†

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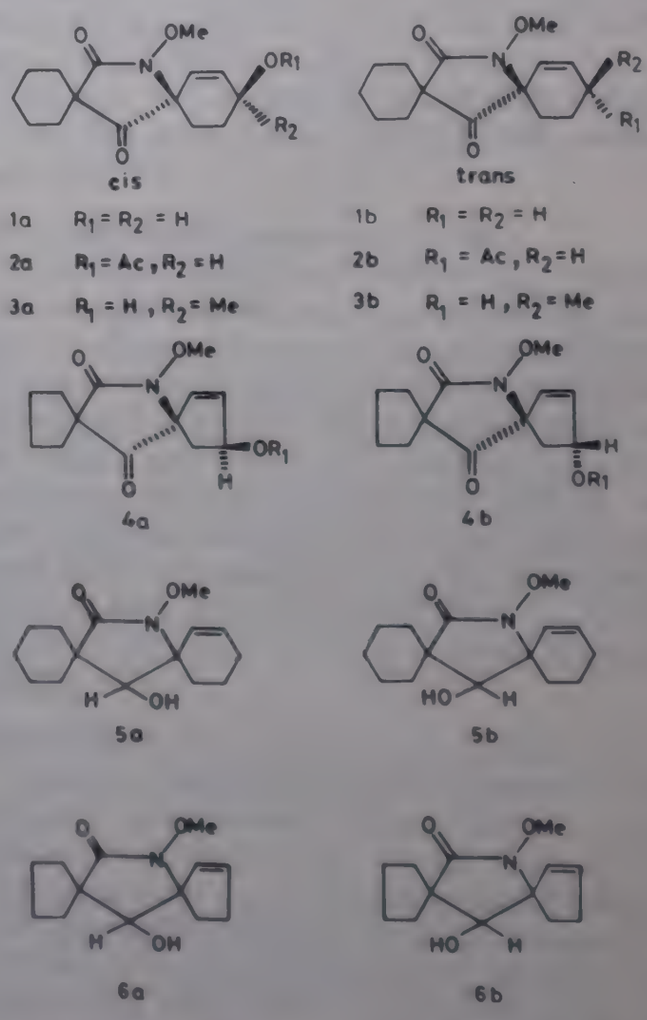
Received 26 *December* 1985; *revised and accepted* 8 *July* 1986

The positive and negative ion chemical ionization behaviour of certain 11-substituted-14-methoxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-diones has been found to be dependent on the stereochemistry of the 11-substituent (R_1 = H, Ac). Elimination of R_1OH is favoured in the *cis*-isomer. Similarly, MNH_4^+/MH^+ ratio in their CI(NH_3) spectra is greater in the *cis*-isomer. The *cis*-isomer is again characterised by less abundant $(M+Cl)^-$ ion compared to that in the *trans*-isomer in the NCI(Cl^-) spectra. The difference in the CI behaviour of the isomers has been explained as arising from the favourable bridging possibly in the MH^+ ion of one of the isomers and also from steric interactions of the 11-substituent and the 14-OMe group. The two pairs of isomeric 7-ols (**5** and **6**) do not show any significant steric effects in their CI spectra.

With the increasing number of reports on the dependence of mass spectral fragmentation behaviour of organic molecules on their configuration, mass spectrometry has become an additional technique for configurational studies[1]. We have recently demonstrated the stereochemical dependence of chemical ionization behaviour of the diastereoisomers of quinine[2]. We have also shown stereospecific adduct ion formation in the positive and negative chemical ionization mass spectra of *E*- and *Z*-triarylpropenones[3] and triaryl-nitrocyclohexenes[4]. As an extension of our studies on the stereochemical applications of mass spectrometry we have now examined the CI behaviour of a number of isomeric hydroxylated 14-methoxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-diones and their derivatives. The results of the present study of their positive and negative ion CI spectra are reported here.

The ion abundances in the CI(CH_4) spectra of **1-6** are given in Table 1. The $(M+C_2H_5)^+$ ions, the abundances of which are not stereospecific, are not included. It is clear from Table 1 that the loss of R_1OH depends on the stereochemistry of the OR_1 group. The $(MH-R_1OH)^+$ ion is more abundant in the *cis*-isomer than in the *trans*-isomer. It may be noted here that these steric differences are absent in the isomeric 7-hydroxyl compounds (**5** and **6**). Stereochemical differences are also observed in the CI(NH_3) spectra of the isomeric compounds **1-4**. The NH_4^+ adduction/MH^+ ion ratio is higher in the *cis*-isomers. Again as observed under CI(CH_4) conditions, the 7-hydroxy compounds **5** and **6** do not show any steric effects in their CI(NH_3) spectra.



As these molecules contain a number of heteroatoms, protonation can occur at any one of them and thus the MH^+ ion would consist of a mixture of ionic structures. Since there is no loss of MeOH from the MH^+ ion in **1-4**, the OMe group does not appear to be involved in protonation or proton bridging[5] in these compounds. As the observed differences are in the

† CDRI Communication No. 3756.

Table 1 — Relative Abundances (%) of MH^+ and $(MH-R_1OH)^+$ in the CI (CH_4) Spectra of **1-6**

Compd	Ions			
	Isomer-a, *cis*		Isomer-b, *trans*	
	MH^+	$(MH-R_1OH)^+$	MH^+	$(MH-R_1OH)^+$
1	280 (61.7)	262 (100)	280 (100)	262 (60.3)
2	322 (37.1)	262 (100)	322 (64.7)	262 (100)
3	294 (32.0)	276 (100)	294 (100)	276 (95.8)
4	252 (54.5)	234 (100)	252 (100)	234 (80.6)
5	266 (100)	248 (9.1) 234[a] (6.2)	266 (100)	248 (13.2) 234[a] (8.2)
6	238 (100)	220 (18.0) 206[a] (11.2)	238 (100)	220 (16.5) 206[a] (8.0)

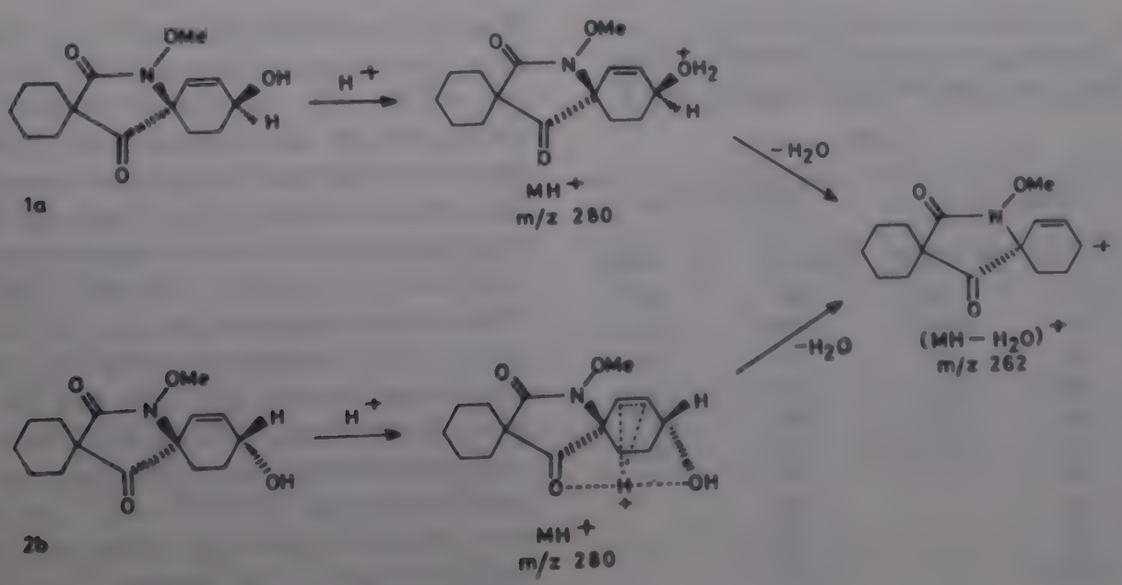
[a] $(MH-MeOH)^+$

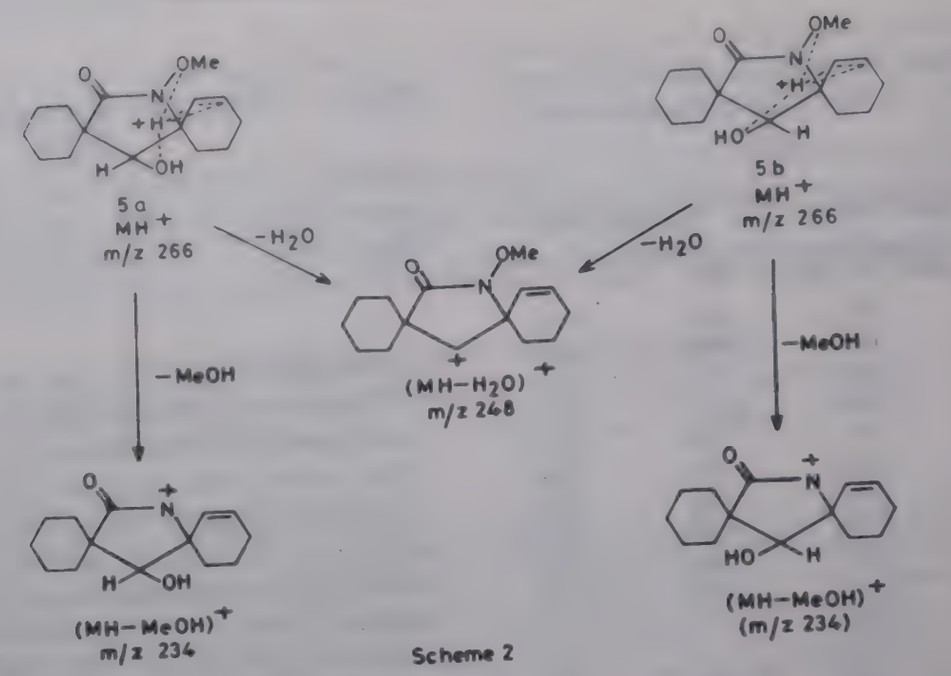
Table 2 — MNH_4^+/MH^+ Ratios in the CI (NH_3) Spectra of **1-6**

Compd	**1**	**2**	**3**	**4**	**5**	**6**
Isomer-a *cis*	2.2	4.0	3.7	2.0	0.1	0.4
Isomer-b *trans*	1.4	1.4	1.2	0.9	0.1	0.4

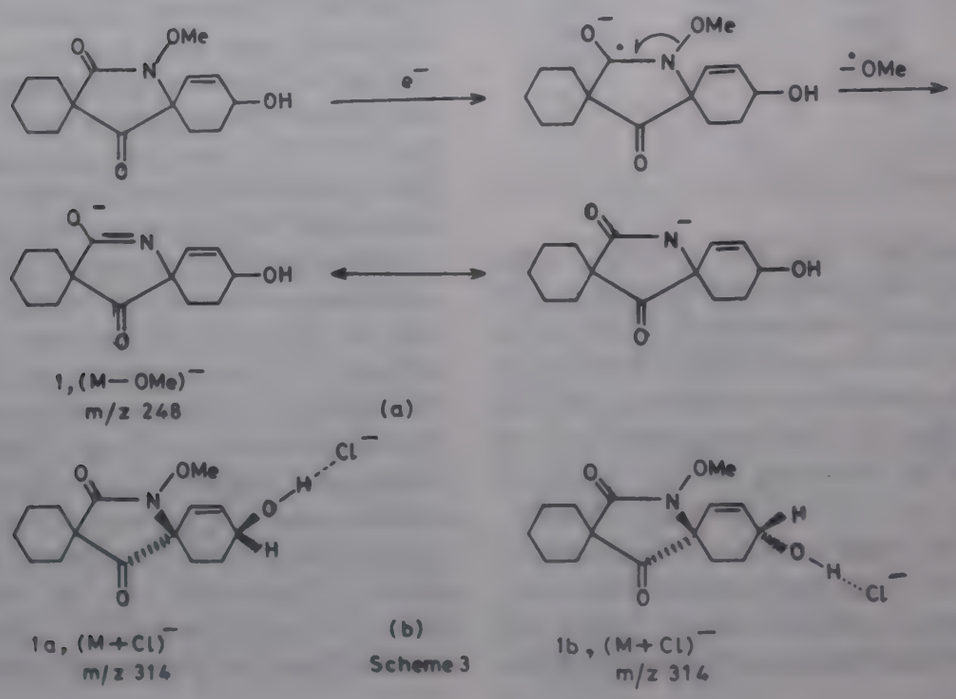
relative stabilities of MH^+ and $(MH-R_1OH)^+$ ions, it is possible that the OR_1 group is involved in proton bridging on protonation of the molecule. Protonation on nitrogen should lead to stable MH^+ ions, while protonation of OR_1 should lead to easy loss of R_1OH from MH^+. In the CI (D_2O) spectrum of **1** $(MD-D_2O)^+$ ion is observed in the place of $(MH-H_2O)^+$ ion in its CI (CH_4) spectrum. The OR_1-protonated MH^+ ion could stabilise by internal proton bridging with the 7-carbonyl oxygen only in the *trans*-isomer (Scheme 1), while in the *cis*-isomer this stabilisation by proton bridging is not possible and as a result $(MH-R_1OH)^+$ ions are more abundant in the *cis*-isomers. The added proton can also involve in bonding with the double bond[6]. As a consequence of these interactions, the proton affinity of the *trans*-isomers will be greater than that of the corresponding *cis*-isomers. This is reflected in the CI (NH_3) spectra which show more abundant MNH_4^+ ions in the *cis*-isomers (Table 2). As observed under CI (CH_4) conditions, the $(MH-H_2O)^+$ ion is also more abundant in *cis*-isomer. These steric effects are not expected in the 7-hydroxy compounds as borne out by the CI results of **5** and **6**. However, unlike compounds **1-4**, these compounds (**5** and **6**) show $(MH-MeOH)^+$ ions in their CI (CH_4) spectra suggesting protonation of OMe group which could involve a proton bridging between the 7-OH and the OMe group (Scheme 2).

The negative ion electron impact spectra of these compounds show only $(M-OMe)^-$ and NCO^- ions with no difference between the isomers. Electron capture by C_{15}-carbonyl oxygen followed by loss of OMe leads to a stable anion (Scheme 3a). However, as observed in the case of *E*- and *Z*-triarylpropenones[3], stereochemical differences could become apparent if another competing pathway for the formation of an adduct ion is possible in the system. Table 3 shows the relative abundances of the $(M-OMe)^-$ and $(M+Cl)^-$ ions in the NCI (Cl^-) spectra of **1-6**. The acetate (**2**) did not give chloride attachment spectra.





Scheme 2



Scheme 3

Table 3 — Relative Abundances (%) of $(M + Cl)^-$ and $(M - OMe)^-$ Ions in the NCI (Cl^-) Spectra of **1-6**

Compd	Ions			
	Isomer-a, *cis*		Isomer-b, *trans*	
	$(M + Cl)^-$	$(M - OMe)^-$	$(M + Cl)^-$	$(M - OMe)^-$
1	314 (100)	248 (48.1)	314 (100)	248 (12.3)
3	328 (100)	262 (33.5)	328 (100)	262 (6.2)
4	286 (100)	220 (51.5)	286 (100)	220 (8.0)
5	300 (100)	—	300 (100)	—
6	272 (100)	—	272 (100)	—

There is a consistent difference in the abundances of these ions between the isomers of **1-4**. The abundance of $(M + Cl)^-$ ion relative to that of $(M - OMe)^-$ ion is more for the *trans*-isomers. Chloride attachment ions are formed through hydrogen bonding with the most acidic hydrogen in a molecule[7]. In these hydroxy compounds the site of attachment would be the 11-hydroxy hydrogen in **1-4** and 7-OH in **5** and **6**. The lesser abundance of the $(M + Cl)^-$ ion in the *cis*-isomer of **1-4** could be explained by invoking steric interactions between the OMe and the 11-hydroxy group in this isomer (Scheme 3b). The occurrence of such steric interactions in the *cis*-isomer has earlier been shown by a ^{13}C NMR study[8]. It is interesting to note here that eventhough similar steric interactions were proposed in the isomeric 7-ols based on ^{13}C NMR results[9], no stereochemical differences could

be observed in their NCI (Cl^-) spectra as both the isomers of **5** and **6** gave only $(M+Cl)^-$ ions.

Experimental Procedure

The preparation of these compounds has been described elsewhere[8-10]. The mass spectra were recorded on a Jeol D-300 mass spectrometer. A mixture of chloroform-methanol (1:10) was used as the source of Cl^- ions for negative chemical ionization. The samples were introduced through the direct inlet system and heated to 50°C. The ion source conditions were: electron energy, 200 eV; emission current, 300 μA; temperature, 150°C; and source housing pressure, 1.5×10^{-5} torr.

Acknowledgement

We are grateful to RSIC, Lucknow for providing facilities to carry out the mass spectral studies.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1228-1230

Carbon-13 NMR Spectral Investigations: Part 13—Yb $(fod)_3$-induced Carbon-13 NMR Shift Studies on Some Benzopyrone Derivatives†

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Received 14 *March* 1986; *accepted* 14 *May* 1986

The Yb $(fod)_3$-induced shifts have been utilized for the definitive carbon-13 signal assignments for chromone, chromanone, chroman-4-ol, flavone, flavanone and flavan-4-ol derivatives, leading to the revision of several earlier reported assignments. The carbon-13 signal displacement associated with acetylation and trichloroacetylcarbamate formation have also been discussed.

Derivatives of the 4*H*-1-benzopyran-4-one or chromone, ring system are widely encountered as natural products. In particular, many substituted 2- and 3-phenyl-chromones (flavones and isoflavones), together with related systems containing a reduced heterocyclic ring, are of importance in medicinal chemistry[1,2]. Carbon-13 NMR spectra of a wide variety of such compounds have been discussed[3,4]. The use of Yb$(fod)_3$-induced shift (LIS) procedure for structural and signal assignment has been recently emphasized[5-7] and herein the LIS studies have been extended to chromone derivatives where a competition between the binding abilities of ethereal oxygen and keto or hydroxyl group is expected[8].

Materials and Methods

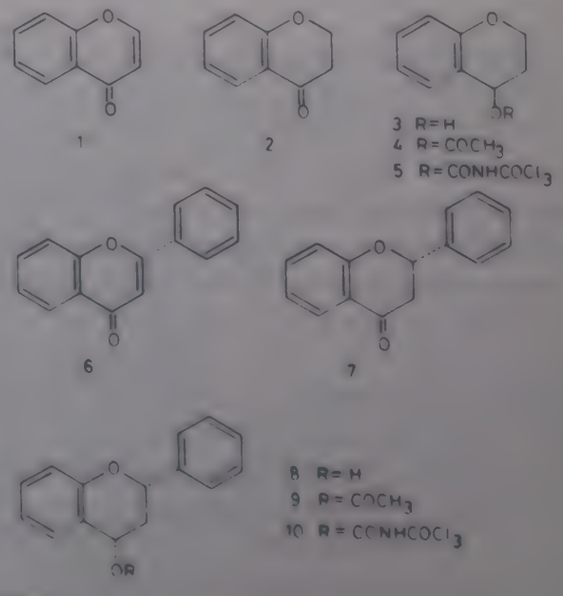
Substrates were either available commercially or prepared by $NaBH_4$ reduction of respective ketones while acetylation of the hydroxy compounds yielded acetyl derivatives. LIS measurements[5,6] were performed by adding Yb$(fod)_3$ (upto 10 ml %) in 4-7 increments (by weight) to substrate (1-2 mmol) in $CDCl_3$ (1.3-1.5 ml). The ^{13}C NMR spectra were recorded on a Bruker Hx-90 or WH-90 NMR spectrometer at 22.63 MHz in the PFT technique, usually with 20° pulse angles, 0.68 s acquisition time for 8 K/4 K spectra, digital resolution of 0.05 ppm at 300 ± 5 K and TMS as internal reference. LIS for different nuclei were usually obtained by least square analysis yielding at least correlation coefficient $r > 0.99$ for RS > 30%, $r > 0.94$ for RS > 10% and $r > 0.89$ for RS > 1%.

The bound shifts calculated for 1:1 LSR-substrate complex for the functional carbon atom (C-α) were set to 100% and relative shifts for other carbon atoms were determined as these were of great significance in establishing stereochemical environment[6-9].

Results and Discussion

The carbon-13 chemical shifts, bound shifts for 1:1 Yb$(fod)_3$-substrate complex and relative shifts (RS)‡ for chromone (**1**), chromanone (**2**), chromanan-4-ol (**3**), flavone (**6**), flavanone (**7**) and flavan-4-ol (**8**) are given in Table 1. These results show almost negligible binding ability of ethereal oxygen as compared to that of the keto group in **1**, **2**, **6** and **7** and of hydroxyl group in **3** and **8**; this was also evident from the comparable RS values for 1-tetralone[9] and **2**. This indicates the existence of half-chair conformation of the heterocyclic ring in the case of **2** which accommodates 2-phenyl substituent in an equatorial position in flavonone (**7**).

Sodium borohydride reduction of **2** and **7** yielded hydroxy derivatives **3** and **8**, respectively. The RS value of 30 for C-2 in the case of **3** corresponded to an



†Part 12 of this series: Schneider H J & Agrawal P K, *Magn Reson Chem*, 24 (1986) (in press)

‡See footnote (a) in Table 1.

Table 1—Carbon-13 Chemical Shifts and $Yb(fod)_3$-induced ^{13}C NMR Shifts (in parentheses) for Chromone and Flavone Derivatives[a]

Carbon atom	1	2	3	4	5[bc]	6	7	8	9	10
C-2	154.91(24)	67.01(21)	61.94(30)	62.07	61.68	163.42(25)	79.47(20)	76.89(23)	76.37	C
C-3	112.52(48)	37.76(44)	30.87(45)	28.40	28.01	107.06(49)	44.53(44)	40.10(51)	35.68	35.16
C-4	176.87(100)	191.60(100)	62.61(100)	65.25	69.15	178.59(100)	191.66(100)	65.77(100)	67.53	70.64
C-5	125.54(31)	127.13(30)	129.73(31)	130.12	130.96	125.85(30)	126.93(30)	129.14(17)	129.54	130.37
C-6	124.82(15)	121.34(15)	120.43(17)	120.37	120.69	125.21(15)	121.47(14)	120.95(14)	120.89	121.15
C-7	133.22(12)	135.84(14)	129.47(15)	130.64	130.96	133.69(13)	136.01(13)	128.17(9)	128.57	128.04
C-8	117.78(13)	117.90(13)	116.93(18)	117.12	116.99	118.18(13)	118.01(13)	116.73(16)	117.12	117.38
C-9	156.05(22)	161.90(23)	154.49(30)	155.34	155.33	156.28(22)	161.43(23)	154.56(27)	155.27	155.53
C-10	124.02(43)	121.34(43)	124.40(45)	120.57	117.31	124.17(42)	120.87(40)	127.00(38)	121.28	119.65
C-1′						131.52(9)	126.07(9)	140.58(12)	140.39	140.12
C-2′						126.33(4)	128.71(6)	126.09(8)	127.39	125.89
C-3′						129.05(4)	128.61(4)	128.62(4)	128.56	128.62
C-4′						131.52(3)	126.07(3)	125.83(3)	126.03	125.89
C-5′						129.05(4)	126.61(4)	128.62(4)	128.56	128.62
C-6′						126.33(4)	128.71(6)	126.09(8)	127.39	125.89

(a) In ppm relative to internal TMS (10%). LIS values are reported to the largest induced shift (S = 100%); the bound shift (ppm) for the carbon showing the largest LIS for the molar ratio [$Yb(fod)_3$: substrate, 1:1); **1** 177.5; **2** 91.09; **3** 108.64; **6** 143.8; **7** 191.66; **8** 105.61.

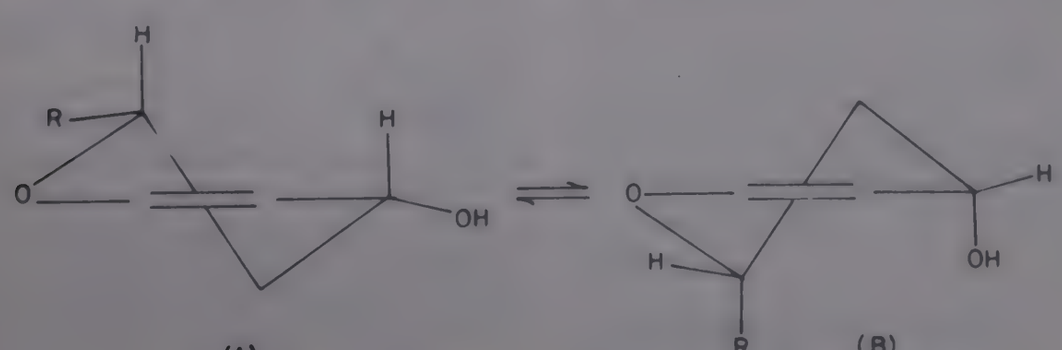
(b) Other signals $OCONHCOCCl_3$: **5** 157.74, 149.35; 91.84; **10** 158.71, 149.48, 92.42.

(c) Superimposed with $CDCl_3$ signals.

equilibrium between conformer (A) and (B) with the major contribution of conformer (B) to pseudoaxially oriented hydroxyl group at C-4. However, in the case of **8**, the 4-OH group acquired predominantly pseudoequatorial orientation, exhibiting anti-periplanar relationship with C-2 (RS value 22) thus, suggesting the major contribution of conformer (A). This was also supported by the almost comparable shift of C-2 resonance of **8** and unsubstituted flavan[10,11], as significant shielding was expected in the case of pseudoaxial orientation of the 4-OH group (γ-effect). These studies were consistent with the reported assignments for chromone[12,13] and chromanone[13,14] but led to the revision of signal assignments for C-5 and C-7, reported by Senda *et al.*[15] for flavan-4-ol (*cis*), as resonance at δ 129.14 showed higher RS value than that for resonance at δ 128.17.

The conversion of **3** into its acetyl derivative (**4**) resulted in the downfield shift of 2.64, 0.91, 0.65, 0.85 ppm for C-4, C-5, C-7 and C-9 resonances and upfield shift of 2.47 and 3.89 ppm of C-3 and C-10 resonances, respectively, thus demonstrating general α- and β-effects[16] in addition to long range effects in *ortho* and *para* positions due to acetylation. This strongly suggested the charge density variation as the origin of the shielding effect of the γ-acyl group[17]. Similar comparison of the chemical shift for **8** and **9** showed comparable results but α- and β-effects differed quite markedly. Thus C-4 showed deshielding (1.76 ppm) whereas C-2 and C-10 resonances appeared upfield by (4.42 and 4.81 ppm). This also reflected[18] the predominant role of the conformer (A) in **8** and an equilibrium between conformers (A) and (B) in **3**. Moreover, this was supported by the substituent-induced shifts (SIS) observed for a variety of chroman derivatives[19] as well as SIS reported for tetralin-1-ol derivatives[9].

In situ derivatization of **3** and **8** with trichloro-



(A) (B)

3 R=H
8 R=Ph

acetylisocyanate (TAI)[20], led to the formation of carbamate derivatives **5** and **10**, respectively which showed chemical shifts alteration in the same direction as caused by acetylation but of a greater magnitude due to higher electron withdrawing nature of $-OCONHCOCCl_3$ substituent. An appreciable deshielding (6.54 and 4.87 ppm) of C-4 resonance and greater shielding (7.09 and 6.18 ppm) for sp^2-β-carbon (C-10) as compared to that of sp^3-β-carbon (C-3) were noticed in **5** and **10** in comparison to **3** and **8**, respectively due to such derivatization. This provided further proof to the signal assignments.

Acknowledgement

The author thanks to Dr Akhtar Husain, for his constant encouragement and Prof. H J Schneider, Universität des Saarlandes, Saarbrückan F R Germany for helpful discussion. Alexander von Humboldt foundation is thanked for the award of a fellowship.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1231-1233

Agents Acting on CNS: Part XXXIV—1,2,3,4,4a,5,6,7-Octahydropyrazino[1,2-*a*]-1-benzazepines†

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Received 4 *September* 1985; *accepted* 1 *May* 1986

3-Substituted 1, 2, 3, 4, 4a, 5, 6, 7-octahydropyrazino [1,2-*a*]-1-benzazepines (II) have been synthesized starting from 2-methylthio-4, 5-dihydro-3*H*-1-benzazepine (III). Some 2-substituted aminoalkyl-2, 3, 4, 5-tetrahydro-1*H*-1-benzazepines (IX) have also been synthesized by condensing 2-aminoalkyl-2, 3, 4, 5-tetrahydro-1*H*-1-benzazepine (V) with different aldehydes followed by LAH reduction of the Schiff bases. None of these compounds exhibits any noteworthy pharmacological activity.

In earlier work[1] carried out in this laboratory it was found that certain 3-substituted 2, 3, 4, 4a, 5, 6-hexahydro-1*H*-pyrazino [1, 2-*a*]quinolines (I) possess marked antidepressant and hypotensive activity. These encouraging results prompted us to synthesise their ring-B homologs, viz. 1, 2, 3, 4, 4a, 5, 6, 7-octahydropyrazino [1,2-*a*]benzazepines (II), via a sequence of reactions outlined in Chart 1.

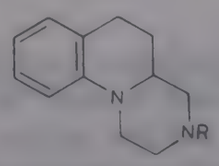
2-Methylthio-4, 5-dihydro-3*H*-1-benzazepine (III) was reacted with $CH_3NO_2/C_2H_5NO_2$ to give IVa/IVb, which on LAH reduction gave 2-aminoalkyl-2, 3, 4, 5-tetrahydro-1*H*-1-benzazepines (Va/Vb). The benzoyl derivative of Va on condensation with ethylene oxide gave 1-β-hydroxyethyl-2-benzoyl-aminomethyl-2, 3, 4, 5-tetrahydro-1*H*-1-benzazepine (VII) which on treatment with 48% HBr gave the octahydro-pyrazinobenzazepine (VIII). In an alternative attempted synthesis of II, 2-chloro-4, 5-dihydro-3*H*-1-benzazepine obtained from 2-oxo-4, 5-dihydro-3*H*-1-benzazepine and PCl_5, was reacted with KCN or NaCN under a variety of conditions but 2-cyano-4, 5-dihydro-3*H*-1-benzazepine thus formed could not be obtained in a pure state.

The IR spectrum of VIII displayed Bohlmann bands[2a,b] around 2800 cm^{-1} suggesting the stereochemistry at B/C ring junction to be *trans*. In the PMR spectrum of 3-formyl derivative (IIa), the 4a-H appeared at τ 5.8, separate from the rest of the protons, with a band width of approximately 32Hz, suggesting its axial geometry which is in conformity with the assignment of *trans* stereochemistry at B/C ring junction for VIII from IR spectrum. Further support for this assignment came from the mass spectrum of VIII which showed a much more intense (M^+-1) ion peak than M^+-ion peak, which had been shown[3] to be diagnostic for quinolizidines with bridgehead proton *trans* to the nitrogen lone pair.

Compounds IIa-g were prepared from VIII by essentially known methods of synthesis.

Compounds (Va, b) were condensed with acetaldehyde, benzaldehyde and phenylacetaldehyde to give the corresponding schiffs bases which were reduced with LAH to yield 2-substituted aminoalkyl-2, 3, 4, 5-tetrahydro-1*H*-benzazepines (IX, a, b) (Table 1).

All these compounds were screened for their pharmacological activity, but none of them showed any significant activity, indicating that a pyrazino-quinoline ring system is essential for hypotensive activity in compounds of type (I).



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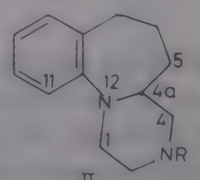


II

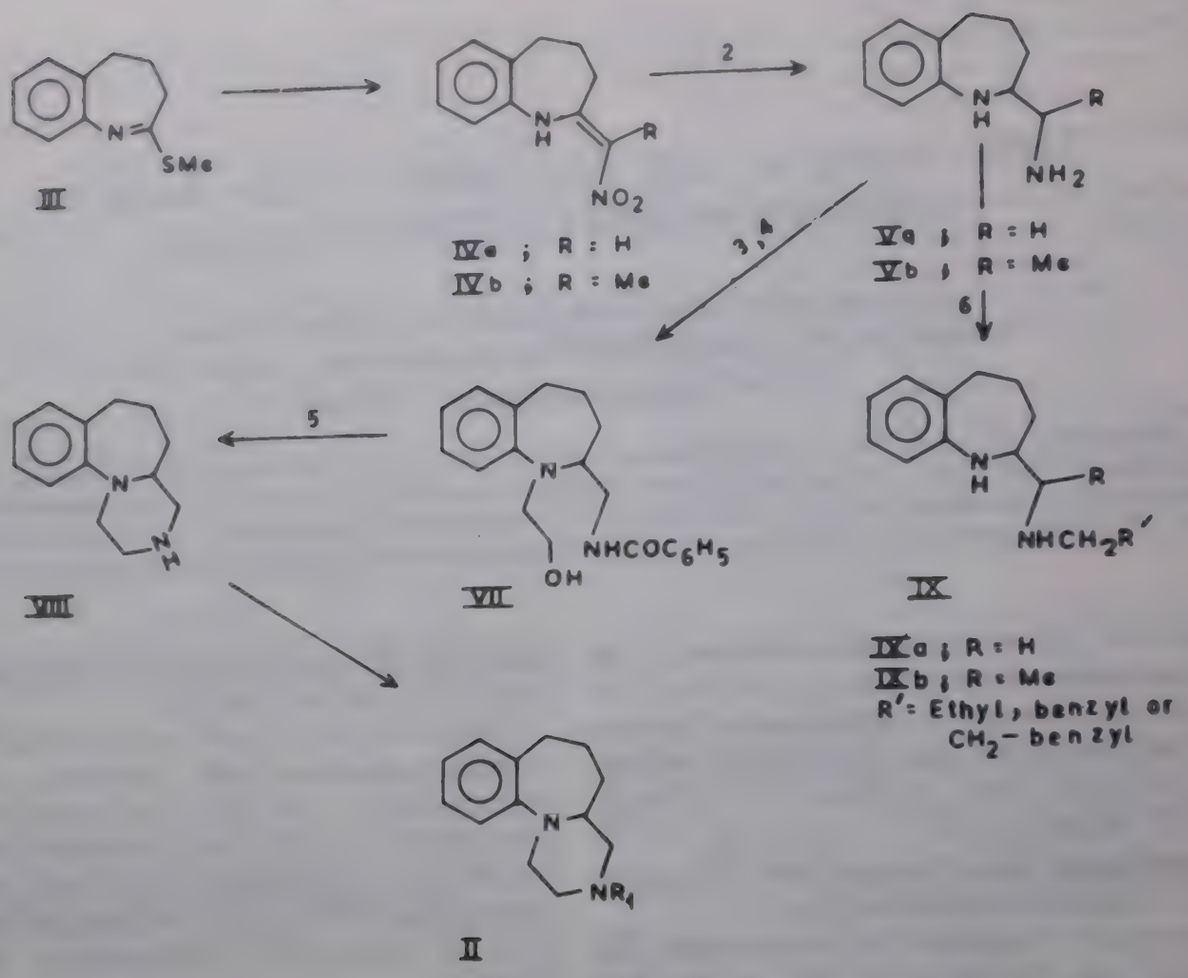
Experimental Procedure

The reaction product were routinely checked by IR on a Perkin-Elmer 337 grating spectrophotometer. The PMR spectra were taken on a Varian A 60D instrument using TMS as an internal reference and chemical shifts are expressed in τ scale. Melting points were determined in a sulphuric acid bath and are uncorrected. The compounds were routinely checked by TLC on silica gel plates. The elemental analysis of the compounds were within 0.3% of the expected value.

2-Aminomethyl-2,3,4,5-tetrahydro-1H-1-benzazepine (Va)

A solution of 1-(1, 3, 4, 5-tetrahydro-1-benzazepine)-2-nitroethylene[4] (IVa, 2 g, 0.01 mol) in

†CDRI Communication No. 3561.



1. RCH_2NO_2; 2. LAH; 3. C_6H_5COCl; 4.  ; 5. 48% HBr; 6. R^1CHO

II b, R_1 = Me ; c, $R_1 = (CH_2)_2COMe$; d, $R_1 = (CH_2)_2CH(OH)Me$; e, $R_1 = (CH_2)_2$-  ;

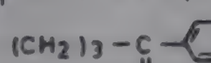
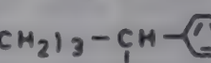
f, $R_1 = (CH_2)_3$-  ; g, $R_1 = (CH_2)_3$- 

Chart 1

dry ether (30 ml) was added dropwise with stirring to a suspension of LAH (0.04 mol) in ether. The stirring was continued for 20 hr and the reaction product worked-up in the usual manner to give Va in 92% yield, b.p. 100°/8 mm; benzoyl derivative (VI) m.p. 143°; IR (KBr): 3350, 2900, 1650; PMR ($CDCl_3$): 2.1 (*m*, 2H, ArH 2', 6'), 2.3-3.5 (*m*, 8H, rest *ArH* + N*H*), 8.2 (*m*, 4H, H-3, H-4).

Similarly Vb was prepared from 1-(1, 3, 4, 5-tetrahydro-1-benzazepino)-2-nitromethylethylene (IVb); benzoyl derivative, m.p. 225°.

1-β-Hydroxyethyl-2-benzoylaminomethyl-2,3,4,5-tetrahydro-1H-1-benzazepine (VII)

2-Benzoylaminoethyl-2, 3, 4, 5-tetrahydro-1*H*-1-benzazepine (VI) (27 g, 0.1 mol) was dissolved in gl. acetic acid (200 ml), the solution diluted with water (50 ml) and the reaction mixture kept at 0-5° for 48 hr and then at 25-30° for another 48 hr. The reaction mixture was concentrated to almost dryness, the oily mass taken up in ether, washed with water and dried (Na_2SO_4). Evaporation of the solvent gave the required VII as an oil which was purified by chromatography on a silica gel column, yield 91%; IR (neat): 3350, 2900, 1650; PMR ($CDCl_3$): 2.05 (*m*, 2H, ArH, *ortho* to CO group), 2.6 (*m*, 7H, ArH), 6.15-7.5 (*m*, 9H, CH_2 adjacent to N, benzylic CH_2, O*H*, *N*HC*H*), 8.85 (*m*, 6H, rest CH_2).

1, 2, 3, 4, 4a, 5, 6, 7-Octahydropyrazino[1,2-a]-1-benzazepine (VIII)

A mixture of VII (0.01 mol) and 48% HBr (30 ml) was refluxed for 24 hr, cooled, filtered and evaporated to dryness. The residue was treated with aq. NaOH, and extracted repeatedly with ether. The combined extract was dried (Na_2SO_4) and evaporated to give VIII as an oil, b.p. 168°/2×10^{-3} nm; yield 60%; IR (neat): 3350, 2950, 1600; PMR ($CDCl_3$): 2.5-3.35 (*m*, 4H, Ar*H*), 6.2-7.8 (*m*, 10H, H-1, H-2, H-4, H-4a, H-7, NH), 7.8-8.5 (*m*, 4H, H-5, H-6); mass: *m/z* 202 (M^+), 201 (M-1), 186 (M-16).

3-*Methyl*-1,2,3,4,4*a*-5,6,7-*octahydropyrazino*-[1,2-*a*]-1-*benzazepine* (*IIb*)

A mixture of VIII (6.5 mol) and ethyl formate (5 mol) was refluxed for 48 hr. Excess of ethyl formate was evaporated *in vacuo* to afford IIa as an oil. LAH reduction of the formyl derivative gave the required product IIb in 96% yield; hydrochloride, m.p. 210°; IR (neat), 3275, 2910, 1600; PMR ($CDCl_3$): 2.6-3.3 (*m*, 4H, Ar*H*), 5.8 (*m*, 1H, H-4a), 6.5-8.1 (*m*, 8H, H-1, H-2), H-4, H-7), 8.45 (*m*, 4H, H-5, H-6), 7.7 (*s*, 3H, N-CH_3).

3-(3-*Oxobutyl*)-1,2,3,4,4*a*,5,6,7-*octahydro-pyrazino*[1,2-*a*]-1-*benzazepine* (*IIc*)

A mixture of VIII (20 mmol and methyl vinyl ketone (22 mmol) in benzene (20 ml) was stirred at room temperature for 24 hr. The solvent was evaporated *in vacuo* and the product obtained as an oil; hydrochloride, m.p. 175°; yield 67%; IR (neat): 3275, 2950, 1725; PMR ($CDCl_3$): 2.5-3.3 (*m*, 4H, Ar*H*), 6.2-8.2 (m, 16H, H-1, H-2, H-4, H-4a, H-7, $CH_2CH_2COCH_3$), 7.85 (*s*, 3H, $COCH_3$), 8.45 (*m*, 4H, H-5, H-6).

3-(3-*Hydroxybutyl*)-1,2,3,4,4*a*,5,6,7-*octahydro-pyrazino*[1,2-*a*]-1-*benzazepine* (*IId*)

Powdered $NaBH_4$ (10 mmol) was added to IIc (10 mmol) in absolute ethanol (20 ml) at 0°C. The reaction mixture was stirred at room temperature for 16 hr and evaporated to dryness. The residue was taken up in water, extracted with ether, the ether layer dried (Na_2SO_4) and evaporated to give IIc as an oil; hydrochloride, m.p. 160°; yield 91%; IR (neat): 3300, 2950, 1600; PMR ($CDCl_3$): 2.52-3.23 (*m*, 4H, ArH), 5.4 (*m*, 1H, O*H*), 6 (*m*, 1H, H-4a), 6.2-7.75 (*m*, 10H, H-1, H-2, H-4, H-7, H-1'), 7.5-9.0 (*m*, 10H, H-5, H-6, H-2', H-3', H-4').

3-β-(4-*Pyridylethyl*)-1,2,3,4,4*a*,5,6,7-*octahydro-pyrazino*[1,2-*a*]-1-*benzazepine* (*IIe*)

A mixture of 4-vinylpyridine (11 mmol), gl. acetic acid (10 mmol), VIII (10 mmol) and ethanol (30 ml) was refluxed for 20 hr, and the solvent removed under reduced pressure. The residue was rendered alkaline with aq. NaOH, extracted with chloroform and the extract dried (Na_2SO_4). Removal of the solvent gave IIe as an oil; hydrochloride, m.p. 120°; yield 85%; IR (neat): 3275, 2900, 1600; PMR (CCl_4): 1.53 (*dd*, 2H, H-2', H-6', J_{ortho} = 5Hz, J_{meta} = 1Hz), 2.67-3.34 (*m*, 6H, ArH, H-5'), 6.7-8 (*m*, 13H, H-1, H-2, H-4, H-7, H-4a, N-CH_2-CH_2), 8.9 (*m*, 4H, H-5, H-6).

3-(γ-*p-Fluorobenzoylpropyl*)-1,2,3,4,4*a*,5,6,7-*octahydropyrazino*[1,2-*a*]-1-*benzazepine* (*IIf*)

A mixture containing VIII (5 mmol), 3-*p*-fluorobenzoylpropyl chloride (10 mmol), anhydrous K_2CO_3 (5 mmol) and freshly baked NaI (10 mmol) in dry acetone (25 ml) was stirred and refluxed for 24 hr. The reaction mixture was cooled, filtered and evaporated to give IIf as an oil; hydrochloride, m.p. 95°; yield 75%; IR (neat): 3400, 2950, 1710, 1600; PMR ($CDCl_3$): 6.45 (*m*, 1H, 1a-H), 6.61-8.7 (*m*, 18H, H-1, H-2, H-4, H-5, H-6, H-7, N-CH_2-CH_2-CH_2-CO).

3-[γ-(*p-Fluorophenyl*)-6-*hydroxybutyl*]1,2,3,4,4*a*,5,6,7-*octahydropyrazino*[1,2-*a*]-1-*benzazepine* (*IIg*)

$NaBH_4$ reduction of IIf in MeOH yielded IIg as an oil; hydrochloride, m.p. 150°; yield 94%; IR (neat): 3900, 2950, 1600; PMR ($CDCl_3$): 2.4-3.3 (*m*, 8H, ArH), 5.29 (*s*, 1H, O*H*), 5.6-8 (*m*, 12H, H-1', H-2, H-4, H-4a, H-7, N-CH_2-CH_2-CH-OH).

2-*Substituted aminomethyl*-2,3,4,5-*tetra-hydro*-1*H*-1-*benzazepines* (*IXa, b*)

Va/Vb (0.01 mol) and suitable aldehyde (0.01 mol) in dry benzene was stirred for 5 mts and azeotroped with dry benzene till no more water separated. The schiffs base thus obtained were directly reduced by LAH in the usual manner to get the required product IXa, b. The compound IXa (**1-3**) and IXb (**4-6**) were obtained as oils. Their characterization data are recorded in Table 1.

Table 1—Characterization Data of Compounds of Type IXa/IXb

Compd.	R	Mol. formula	Analysis (%)	Found	Reqd
		IXa			
1	CH_2CH_3	$C_{13}H_{20}N_2$	C:	76.9	76.4
			H:	9.6	9.9
				81.1	81.2
2	$CH_2C_6H_5$	$C_{18}H_{22}N_2$		8.5	8.3
3	$CH_2CH_2C_6H_5$	$C_{19}H_{24}N_2$		81.7	81.4
				8.9	8.6
		IXb			
4	CH_2CH_3	$C_{14}H_{22}N_2$		76.9	77.1
				10.3	10.1
5	$CH_2C_6H_5$	$C_{19}H_{24}N_2$		81.2	81.5
				8.3	8.6
6	$CH_2CH_2C_6H_5$	$C_{20}H_{26}N_2$		81.3	81.6
				8.7	8.8

Acknowledgements

The authors are grateful to Dr B N Dhawan for making available pharmacological evaluation results.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1234-1237

Synthesis of 2/9-Substituted Indophenazin-6-acetic Acid α-Aryl/ methylbenzylidenehydrazides, 4-Aryl-1-(indophenazin-6-methylcarbonyl)-3-thiosemicarbazides & 6-(4-Aryl-5-mercapto-4*H*-1,2,4-triazol-3-ylmethyl)indophenazines as CNS Active & Antiinflammatory Agents

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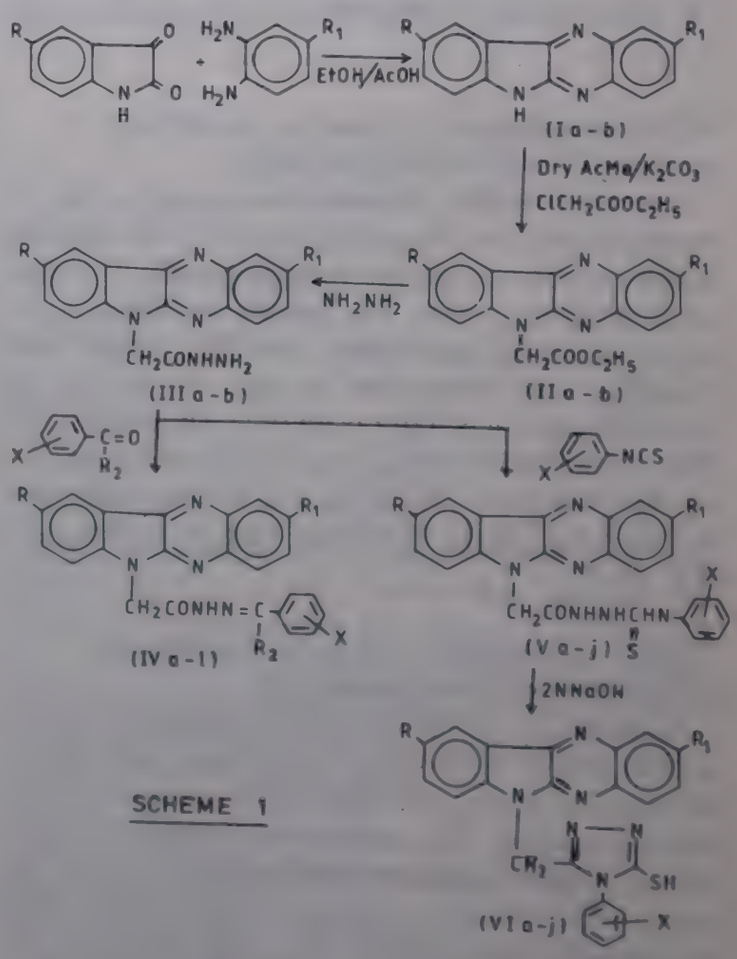
Received 3 *October* 1985; *revised and accepted* 11 *June* 1986

2/9-Substituted indophenazine-6-acetic acid α-aryl/methylbenzylidenehydrazides (IVa-l) and 4-aryl-1-(2/9-substituted indenophenazin-6-methylcarbonyl)-3-thiosemicarbazides (Va-j) have been synthesised by condensing 2/9-substituted indophenazin-6-acetic acid hydrazides(III) with different aryl aldehydes/acetophenones and phenyl isothiocyanates, respectively. All the Thiosemicarbazides (V) undergo cyclisation in 2*N* NaOH to give 2/9-substituted 6-(4-aryl-5-mercapto-4*H*-1,2,4-triazol-3-ylmethyl)indophenazines (VIa-j). All these compounds have been found to be non toxic and CNS active. Most of them show significant protection against carrageenin-induced inflammation.

Recently much interest has been focussed on the psychotropic[1] and antiinflammatory[2] activities of substituted oxo-indoles. Earlier work has shown that CNS depressant[3], anticonvulsant[4] and antiinflammatory[5] properties are associated with substituted indoles. Moreover, compounds having quinazoline as the parent moiety are reported to be useful antiinflammatory agents[6]. On the other hand different triazoles are also reported to possess psychotropic[7] and antiinflammatory[8] properties. The effectiveness of indole and quinazoline moieties towards various CNS disorders prompted the authors to synthesise a number of substituted indophenazines (IV-VI) and evaluate their CNS and antiinflammatory activities.

The reaction sequence leading to the formation of different title compounds, under the methods reported earlier[9] is outlined in Scheme 1. The required 2/9-substituted indophenazines (Ia, b) were prepared by a known method[12] and reacted with ethyl chloroacetate in dry acetone and anhyd. K_2CO_3 to furnish the intermediate 6-carbethoxymethyl-2/9-substituted-indophenazines (IIa, b), which on hydrazinolysis yielded 2/9-substituted-indophenazine-6-acetic acid hydrazides (IIIa, b). The reaction of III with different aryl aldehydes and acetophenones in abs. ethanol gave the desired 2/9-substituted indophenazin-6-acetic acid α-aryl/methylbenzylidenehydrazides (IVa-l; Table 1). The 4-aryl-1-(2/9-substituted indophenazin-6-methylcarbonyl)-3-thiosemicarbazides (Va-j; Table 1) were prepared by condensing III with appropriate phenyl isothiocyanates. Cyclization of V in 2*N* NaOH solution under reflux finally gave the 6-(4-aryl-5-mercapto-4*H*-1,2,4-triazol-3-ylmethyl)-2/9-substituted-indophenazines (VIa-j; Table 1).



SCHEME 1

Structures of all the compounds synthesised were established by elemental analyses and spectral data (IR and PMR).

Pharmacological screening

All the compounds of the series IV, V and VI were screened for their toxicity, gross CNS and antiinflammatory activities in albino mice of either sex. For toxicity test the compounds were administered at doses

Table 1 — Physical Data of Compounds II-VI

Compd	X	m.p.*† °C	Yield (%)	Mol. formula	Found (%)			Calc (%)		
					C	H	N	C	H	N
		R = H; R_1 = Cl								
IIa	—	212	80	$C_{18}H_{14}N_3O_2Cl$	63.6	4.2	12.0	63.6	4.1	12.3
		R = Br; R_1 = H								
IIb	—	240	85	$C_{18}H_{14}N_3O_2Br$	56.2	3.8	10.9	56.3	3.6	10.9
		R = H; R_1 = Cl								
IIIa	—	263	90	$C_{16}H_{12}N_5OCl$	60.1	3.8	21.5	60.0	3.7	21.5
		R = Br; R_1 = H								
IIIb	—	> 290	95	$C_{16}H_{12}N_5OBr$	51.9	3.4	19.1	51.9	3.3	18.9
		$R = R_2$ = H, R_1 = Cl								
IVa	H	> 280	80	$C_{23}H_{16}N_5OCl$	66.5	3.9	16.0	66.7	3.8	16.9
IVb	4-OH	> 280	75	$C_{23}H_{16}N_5O_2Cl$	64.3	3.7	16.2	64.3	3.7	16.3
IVc	4-OCH_3	> 280	65	$C_{24}H_{18}N_5O_2Cl$	64.8	4.0	15.8	64.9	4.1	15.8
IVd	4-$N(CH_3)_2$	> 280	60	$C_{25}H_{21}N_6OCl$	65.8	4.6	18.5	65.7	4.6	18.4
IVe	3-OCH_3, 4-OH	> 280	70	$C_{24}H_{18}N_5O_3Cl$	62.5	4.0	15.3	62.6	3.9	15.2
IVf	3,4-$(OCH_3)_2$	> 280	75	$C_{25}H_{20}N_5O_3Cl$	63.3	4.3	14.8	63.4	4.2	14.8
		$R = R_1$ = Cl, R_2 = CH_3								
IVg	H	> 280	65	$C_{24}H_{18}N_5OCl$	67.3	4.2	16.3	67.3	4.2	16.4
IVh	2-OH	240	65	$C_{24}H_{18}N_5O_2Cl$	64.9	4.0	15.8	64.9	4.0	15.8
IVi	4-CH_3	> 280	60	$C_{25}H_{20}N_5OCl$	68.0	4.5	15.9	68.0	4.5	15.8
IVj	4-NH_2	276	70	$C_{24}H_{19}N_6OCl$	65.0	4.3	18.9	65.1	4.3	19.0
IVk	3-NO_2, 4-Br	> 280	75	$C_{24}H_{16}N_6O_3ClBr$	52.3	3.0	15.3	52.2	2.9	15.2
IVl	4-Cl	> 280	75	$C_{24}H_{17}N_5OCl_2$	62.4	3.6	15.1	62.3	3.7	15.2
		R = H, R_1 = Cl								
Va	H	> 290	75	$C_{23}H_{17}N_6OSCl$	59.9	3.7	18.2	59.9	3.7	18.2
Vb	4-CH_3	> 290	70	$C_{24}H_{19}N_6OSCl$	60.8	4.0	17.8	60.7	4.0	17.7
Vc	4-OCH_3	> 290	80	$C_{24}H_{19}N_6O_2SCl$	58.8	4.0	17.0	58.7	3.9	17.1
Vd	2-OC_2H_5	> 290	65	$C_{25}H_{21}N_6O_2SCl$	59.5	4.0	16.6	59.5	4.1	16.7
Ve	4-Cl	> 290	60	$C_{23}H_{16}N_6OSCl_2$	55.7	3.3	16.9	55.7	3.2	16.9
		R = Br, R_1 = H								
Vf	H	276	70	$C_{23}H_{17}N_6OSBr$	54.6	3.4	16.7	54.7	3.4	16.6
Vg	4-CH_3	290	70	$C_{24}H_{19}N_6OSBr$	55.4	3.7	16.2	55.5	3.7	16.2
Vh	4-OCH_3	265	65	$C_{24}H_{19}N_6O_2SBr$	53.8	3.5	15.8	53.8	3.6	15.7
Vi	2-OC_2H_5	275	75	$C_{25}H_{21}N_6O_2SBr$	54.7	3.8	15.3	54.6	3.8	15.3
Vj	4-Cl	290	60	$C_{23}H_{16}N_6OSClBr$	51.0	3.0	15.5	51.1	3.0	15.6
		R = H, R_1 = Cl								
VIa	H	> 290	80	$C_{23}H_{15}N_6SCl$	62.3	3.5	19.0	62.4	3.4	19.0
VIb	4-H_3	> 290	80	$C_{24}H_{17}N_6SCl$	63.0	3.8	18.4	63.1	3.7	18.4
VIc	4-OCH_3	> 290	75	$C_{24}H_{17}N_6OSCl$	61.0	3.6	17.8	61.0	3.6	17.8
VId	2-OC_2H_5	> 290	70	$C_{25}H_{19}N_6OSCl$	61.7	4.0	17.3	61.7	3.9	17.3
VIe	4-Cl	240	70	$C_{23}H_{14}N_6SCl_2$	57.9	3.0	17.6	57.9	2.9	17.6
		R = Br, R_1 = H								
VIf	H	> 290	80	$C_{23}H_{15}N_6SBr$	56.7	3.0	17.3	56.7	3.1	17.2
VIg	4-CH_3	> 290	75	$C_{24}H_{17}N_6SBr$	57.5	3.4	16.8	57.5	3.4	16.8
VIh	4-OCH_3	> 290	65	$C_{24}H_{17}N_6OSBr$	55.7	3.3	16.3	55.7	3.3	16.2
VIi	2-OC_2H_5	> 290	60	$C_{25}H_{19}N_6OSBr$	56.5	3.6	15.9	56.5	3.6	15.8
VIj	4-Cl	> 290	70	$C_{23}H_{14}N_6SClBr$	53.0	2.8	16.2	52.9	2.7	16.1

*Compounds II and III with $R = R_1$ = H are already reported[14].
†Compounds II and III were recrystallised from ethyl acetate and dioxane, respectively. Compounds IV, V and VI were recrystallised from methanol, gl. acetic acid and ethanol, respectively.

of 215, 464 and 1000 mg/kg body weight of mice intraperitoneally as 5% aq. gum acacia suspension and the ALD_{50} values determined by the known method[10]. For gross CNS observations, compounds were administered at 1/5th of ALD_{50} and behavioural changes in spontaneous motor activity (SMA) and reactivities to sound were noted. The effect on body temperature (hypothermia) was also observed. The antiinflammatory activity at 1/5th of ALD_{50} was evaluated in mice by measuring the percentage protection against the carrageenin-induced paw oedema by the standard method[11]. For comparative study indomethacin (a standard drug) was used at a concentration of 2 mg/kg.

The ALD_{50} values of the compounds IV, V and VI were found to be in the range of 681 to > 1000 mg/kg except for two compounds (VIa; 316 and VIb; 562 mg/kg). Four compounds (Vc and VIe to VIg) were CNS stimulants, whereas all the other compounds were CNS depressants as they increased or decreased the SMA and reactivities to sound and touch, respectively. Hypothermia was also observed for different compounds in the range of 0.2-0.8°C. As regards antiinflammatory activity, all the compounds (IV, V and VI) showed protection against the carrageenin-induced paw inflammation in mice except compounds IVd, IVf, Vd, VIe to VIg. The antiinflammatory activity ranged from 1.4 to 62.2% at 1/5th of ALD_{50} as compared to 37.1% protection shown by indomethacin. The ALD_{50} values and other pharmacological data of compounds IV, V and VI are recorded in Table 2.

Experimental Procedure

M.ps were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 157 spectrophotometer (ν_{max} in cm^{-1}) and PMR spectra in $CDCl_3$, DMSO-d_6 and TFA on a Varian A-90D instrument using TMS as internal standard (chemical shift in δ, ppm). Purity of the compounds was checked by TLC on plates coated with silica gel-G (0.25 mm) using benzene-methanol (99:1) as irrigant.

2/9-Substituted indophenazines[12] (Ia, b) and substituted phenyl isothiocyanates[13] were prepared by known methods.

6-Carbethoxymethyl-2/9-substituted-indophenazines (IIa, b; Table 1)

A mixture of 2/9-substituted indophenazine (I; 0.01 mol) and ethyl chloroacetate (0.015 mol) in dry acetone (200 ml) and K_2CO_3 (0.2 mol) was refluxed for 20 hr. The solvent was removed and the residue treated with cold water. The solid thus obtained was filtered and recyrstallised from ethyl acetate to give IIa or IIb. IR: 3010, 2910 (C—H), 1730 (C = O), 1610 (C = N). The PMR ($CDCl_3$) spectrum of IIa exhibited signals at 7.72-6.94 (*m*, 7H, Ar-*H*), 5.22 (*s*, 2H, CH_2CO), 4.15 (*q*, *J* = 3.15 Hz, 2H, $COOCH_2$) and 1.50 (*t*, *J* = 3.15 Hz, 3H, $COOCH_2CH_3$).

2/9-Substituted indophenazine-6-acetic acid hydrazides (IIIa, b; Table 1)

To a refluxing solution of II (0.1 mol) in abs. ethanol (150 ml), was added hydrazine hydrate (99%; 0.15 mol), and the solution refluxed for 6 hr. The solvent was removed and the solid filtered and recrystallised from dioxane to give IIIa or IIIb; IR: 3500, 3450 (N—H), 3050, 2900 (C—H), 1660 (C = O) and 1610 (C = N). The PMR (DMSO-d_6) spectrum of IIIa exhibited signals at 8.12 (*s*, 1H, CO—NH), 7.88 (*s*, 2H, NH_2), 7.60-6.78 (*m*, 7H, Ar-*H*) and 5.20 (*s*, 2H, NCH_2CO).

2/9-Substituted indophenazin-6-acetic acid αaryl/methylbenzylidenehydrazides (IVa-l; Table 1)

An equimolar (0.0025 mol) mixture of III and aryl aldehyde or substituted acetophenone in abs. ethanol (50 ml) containing 2-3 drops of gl. acetic acid was refluxed for 4 hr, and solvent removed. The separated solid was filtered and recrystallised from methanol to give IV; IR: 3250 (N—H), 3050, 2900 (C—H), 1660 (C = O), 1620, 1610 (C = N) and 1580 (N—H bending); PMR ($CDCl_3$) of IVa: 8.10 (*s*,1H, N—H), 7.82-6.62 (*m*, 12H, Ar-*H*), 6.24 (*s*, 1H, N = C*H*-Ar) and 5.22 (*s*, 2H, N—CH_2CO); PMR ($CDCl_3$) of IVi: 8.10 (*s*, 1H, N—H), 7.84-6.56 (*m*, 11H, Ar-*H*), 5.20 (*s*, 2H, NCH_2CO), 2.96 (*s*, 3H, N = C—CH_3) and 2.01 (*s*, 3H, CH_3).

4-Aryl-1-(2/9-substituted indophenazin-6-methylcarbonyl)-3-thiosemicarbazides (Va-j; Table 1):

To a boiling solution of III (0.0025 mol) in abs. ethanol (30 ml) was added an appropriate phenyl isothiocyanate (0.0025 mol), and the reaction mixture refluxed for 1 hr, concentrated and cooled. The separated solid was filtered and recyrstallised from gl. acetic acid to give V; IR: 3200 (N—H), 3040, 2900 (C—H), 1660 (C = O), 1600 (C = N) and 1220 (C = S); PMR (TFA) of Va: 8.12-7.00 (*m*, 15H, 12 Ar-*H* and CON*H*N*H*CSN*H*Ph) and 5.22 (*s*, 2H, NHC_2CO).

6-(4-Aryl-5-mercapto-4H-1,2,4-triazol-3-ylmethyl)-2/9-substituted-indophenazines (VIa-j; Table 1)

A solution of V (0.0025 mol) in 2*N* NaOH (20 ml) was refluxed for 4 hr, cooled, poured into ice cold water (50 ml) and neutralized with acetic acid. The precipitate was filtered, washed with water and recyrstallised from ethanol to get VI; IR: 3450 (S—H), 3010, 2910 (C—H) and 1600 (C = N); PMR (TFA) of VIa:

Table 2 — ALD_{50} Values, Gross CNS Observations and Antiinflammatory Activity of the Compounds IV, V and VI

Compd	ALD_{50} mg/kg	Gross CNS observations*			Antiinflammatory activity (% protection)
		SMA & reactivity	Writhing	Hypothermia (°C)	
IVa	> 1000	d	(−)	0.3	31.1
IVb	> 1000	d	(+)	0.6	1.5
IVc	> 1000	d	(−)	0.3	1.4
IVd	> 1000	d	(+)	0.5	(−)
IVe	> 1000	d	(−)	0.3	19.0
IVf	> 1000	d	(−)	0.3	(−)
IVg	> 1000	d	(−)	0.5	29.2
IVh	681	d	(+)	0.2	40.2
IVi	1000	d	(+)	0.2	3.7
IVj	1000	d	(+)	0.8	19.2
IVk	681	d	(−)	0.4	13.0
IVl	> 1000	d	(+)	0.4	27.9
Va	> 1000	d	(−)	0.6	23.8
Vb	> 1000	d	(−)	0.4	21.6
Vc	> 1000	i	(−)	0.4	16.0
Vd	> 1000	d	(−)	0.5	(−)
Ve	> 1000	d	(−)	0.2	26.6
Vf	> 1000	d	(+)	0.4	20.1
Vg	> 1000	d	(+)	0.4	62.2
Vh	> 1000	d	(−)	0.8	14.7
Vi	> 1000	d	(+)	0.3	55.2
Vj	> 1000	d	(+)	0.5	19.2
VIa	316	d	(+)	0.4	12.5
VIb	562	d	(−)	0.3	31.8
VIc	> 1000	d	(−)	0.6	43.5
VId	681	d	(−)	0.4	45.8
VIe	681	i	(+)	0.4	(−)
VIf	> 1000	i	(+)	0.2	(−)
VIg	> 1000	i	(+)	0.2	(−)
VIh	> 1000	d	(+)	0.2	13.3
VIi	> 1000	d	(+)	0.2	58.0
VIj	> 1000	d	(+)	0.2	51.7
indo-methacin	—	—	—	—	37.1

*d = Decreased; i = increased; (+) = present; (−) = absent.

8.26 (*s*, 1H, S—H), 8.02-7.15 (*m*, 12H, Ar-*H*) and 5.22 (*s*, 2H, NCH_2).

Acknowledgement

Thanks are due to Prof. B N Dhawan, Head, Pharmacology Department, CDRI, Lucknow for providing bioassay facilities. One of us (R R M) is thankful to CSIR, New Delhi for the award of a senior research fellowship.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1238-1242

Syntheses of 1-Substituted 4-Arylhydrazono-3-methyl-2-pyrazolin-5-ones & 1-Substituted 4-Arylazo-3,5-dimethylpyrazoles as Potential Antiinflammatory Agents†‡

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Received 26 *July* 1985; *revised and accepted* 20 *May* 1986

A number of 1-substituted 4-arylhydrazono-3-methyl-2-pyrazolin-5-ones (**3-32**) and 1-substituted 4-arylazo-3,5-dimethylpyrazoles (**35-40**) have been prepared and their structures established on the basis of elemental analyses and spectral data (IR and PMR). Some of the compounds exhibit significant antiinflammatory activity against the carrageenin-induced edema in right hind paw of albino mice at 200 mg/kg dose.

Prompted by the antiinflammatory activity of some pyrazolones[1-5] and in continuation of our studies[6-8] on 2-pyrazolin-5-ones we undertook the syntheses of a new series of 1-substituted 4-arylhydrazono-3-methyl-2-pyrazolin-5-ones (**3-32**) and 1-substituted 4-arylazo-3,5-dimethylpyrazoles (**35-40**).

The reaction of ethyl α-arylazo-β-oxobutyrates (**1**, **2**) with hydrazines and benzenesulphonhydrazide afforded the corresponding 4-arylhydrazono-3-methyl-2-pyrazolin-5-ones (**3-8**; Scheme 1; Table 1). A similar reaction of β-arylazoacetylacetone (**33**, **34**) gave the corresponding 4-arylazopyrazoles (**35-40**; Scheme 2; Table 1).

Compounds **3**, **4**, **6** and **7** were found to be identical with those obtained by coupling the diazonium salts of 4-alkoxy-2-nitroanilines with 3-methyl-2-pyrazolin-5-ones (I; R = H or C_6H_5), which in turn were obtained by the general procedure involving treatment of ethyl acetoacetate with hydrazine or phenylhydrazine[3].

A series of 1-acetyl-(**9**,**10**), 1-chloroacetyl-(**11**, **12**) and 1-hydroxymethyl-4-arylhydrazono-3-methyl-2-pyrazolin-5-ones (**13**, **14**) were prepared by the interaction of **3** or **6** with acetic anhydride, chloroacetyl chloride or formalin (Scheme 1).

Trials to cyclise **11** (R = CH_3; X = Cl) to the possible 6-methyl-7-(4-methoxy-3-nitrophenylhydrazono)-2,3,7,7a-tetrahydropyrazolo[5,1-*b*]oxazol-3-one (II; R = CH_3) by heating with acetic anhydride and anhyd. sodium acetate, effected replacement of the chloroacetyl group by an acetyl group yielding the compound **9**. Attempt to bring about cyclisation by warming in dry pyridine resulted in the elimination of the chloroacetyl group with the formation of **3**.

Some Mannich bases (**15-32**; Table 1) were prepared by the interaction of **3** or **6** with appropriate amines and formalin. These bases were also prepared by heating 1-hydroxymethyl derivatives (**13**, **14**) with appropriate amines (Scheme 1).

Pharmacological testing

Albino mice weighing 20-30 g, were used and divided into groups of 6 animals each. Carrageenin (1%) suspension was injected under the plantar aponeurosis of the right hind paw[9]. The test compounds were suspended in 0.5% carboxymethylcellulose and injected i.p. in a dose of 200 mg/kg to a group of 6 animals one hour before carrageenin injection. The control group of 6 mice received an equivalent amount of 0.5% carboxymethylcellulose. The mean increase in the paw weight due to carrageenin induced-edema was determined[10] before and 4 hours after carrageenin treatment, and was used to calculate the antiinflammatory activity of the compounds tested. Phenybutazone (200 mg/kg, i.p.) was used as a reference drug for comparative evaluation (Table 2).

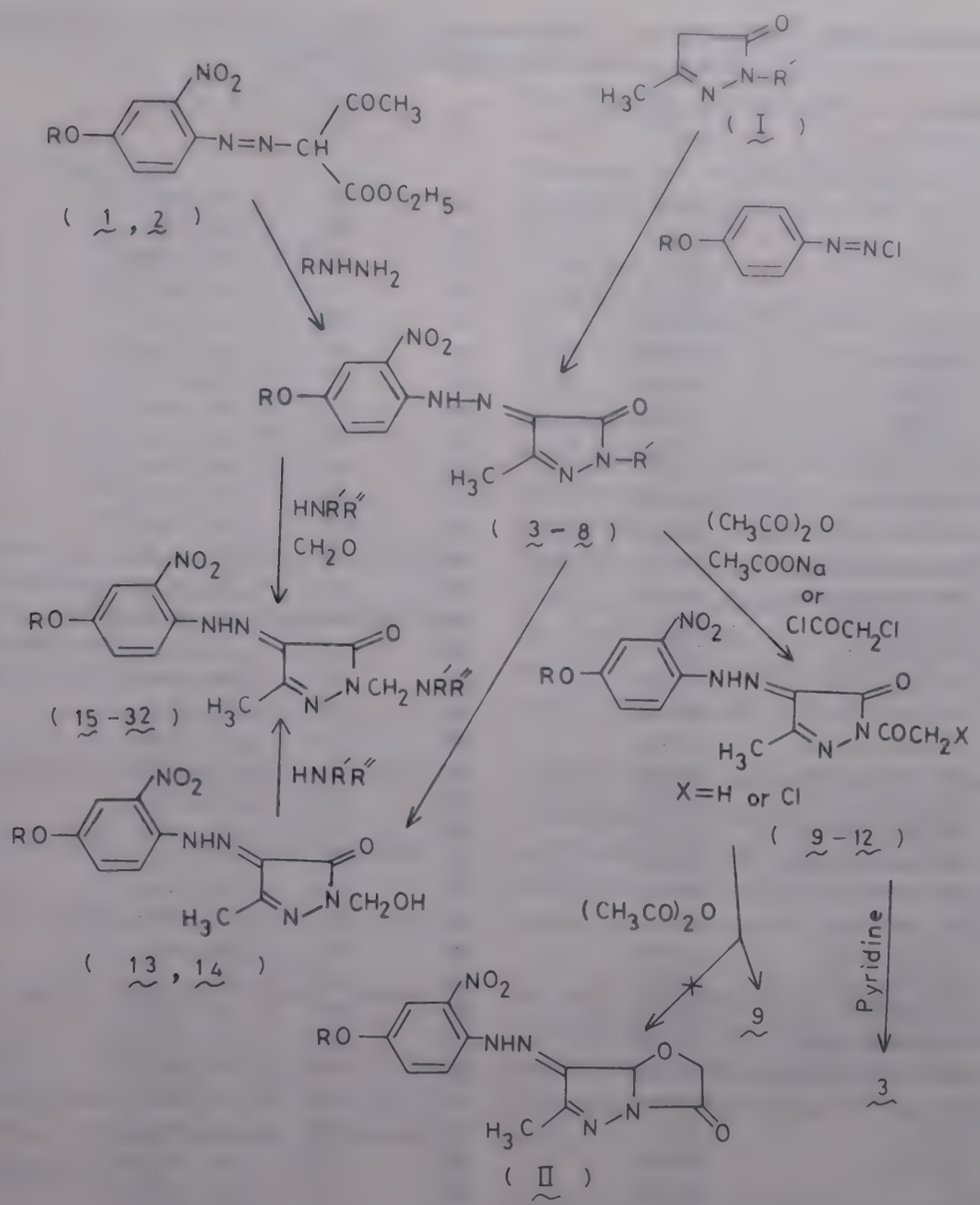
Acute toxicity (LD_{50}) of compounds **3**, **6**, **14** and **23**, which showed significant antiinflammatory activity, was determined by Litchfield and Wilcoxon procedure[11] in uniformly equal sized random groups of mice receiving graded doses ranging from 500-5000 mg/kg body weight i.p. The LD_{50} values were found to be 750 mg/kg for **3**, 720 mg/kg for **6**, 690 mg/kg for **14** and 730 mg/kg for **23**.

Experimental Procedure

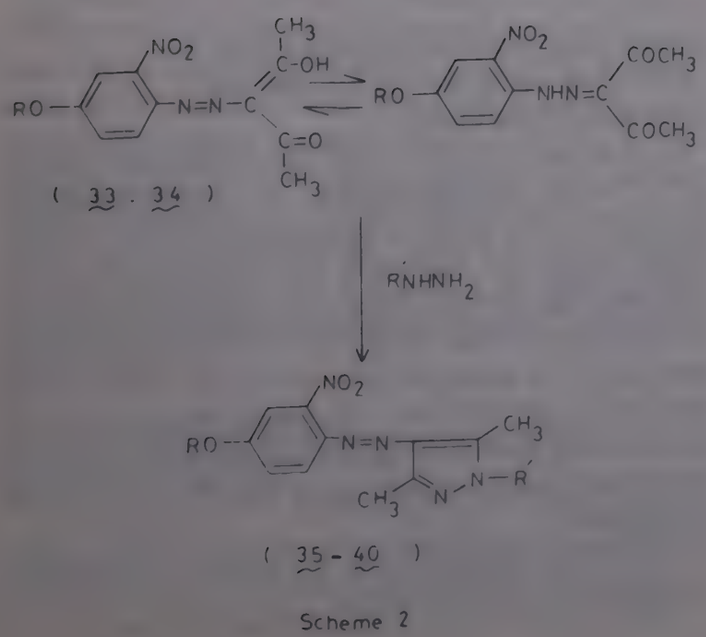
Melting points are uncorrected. IR spectra were recorded in KBr on a Pye-Unicam Sp 2000

†Part XIII of the series "Pyrazolone Derivatives", for Part XII, see ref. 8.

‡Presented at the 2nd Cyprus Conference on New Methods in Drug Research, Limassol, Cyprus, April 14-19 (1985), p. 29.



Scheme 1



Scheme 2

spectrophotometer, and PMR spectra in DMSO-d_6 on a Varian EM-390 90 MHz NMR spectrometer using TMS as an internal standard.

Ethyl α-arylazo-β-oxobutyrates (**1**, **2**) *and β-arylazoacetylacetone* (**33**, **34**)

A solution of 4-methoxy- or 4-ethoxy-2-nitroaniline (0.01 mol) in gl. acetic acid (20 ml) and conc. HCl (30 ml) was cooled in an ice-bath to 0-5°, and a cold solution of sodium nitrite (0.69 g; 0.01 mol) in water (50 ml) added to it dropwise with stirring and cooling. After the addition was over, the solution was set aside for half an hour and rendered alkaline to congo red with saturated solution of sodium acetate. The alkaline diazonium salt solution was dropped over a period of 1 hr into a cold slurry of ethyl acetoacetate or acetylacetone (0.01 mol), sodium acetate (2 g) solution

Table I — Characterisation Data of 1-Substituted 3-Arylhydrazono-3-methyl-2-pyrazolin-5-ones (**3-32**) and 1-Substituted 4-Arylazo-3,5-dimethylpyrazoles (**35-40**)

Compd	R	R′	Crystallized solv.	m.p. °C	Yield (%)	Mol. formula	N (%)* Found	N (%)* Calc.
3	CH_3	H	EtOH – C_6H_6	260	85	$C_{11}H_{11}N_5O_4$	26.6	26.3
4	CH_3	C_6H_5	DMF	236	80	$C_{17}H_{15}N_5O_4$	20.1	19.8
5	CH_3	$SO_2C_6H_5$	EtOH – C_6H_6	180	70	$C_{17}H_{15}N_5O_6S$	16.5	16.8
6	C_2H_5	H	EtOH – C_6H_6	277	95	$C_{12}H_{13}N_5O_4$	24.2	24.1
7	C_2H_5	C_6H_5	EtOH	212	90	$C_{18}H_{17}N_5O_4$	19.3	19.1
8	C_2H_5	$SO_2C_6H_5$	EtOH	191	85	$C_{18}H_{17}N_5O_4S$	15.8	16.2
9	CH_3	$COCH_3$	EtOH	238	70	$C_{13}H_{13}N_5O_5$	21.9	21.9
10	C_2H_5	$COCH_3$	EtOH	209	75	$C_{14}H_{15}N_5O_5$	20.8	21.0
11	CH_3	$COCH_2Cl$	C_6H_6	225	70	$C_{13}H_{12}ClN_5O_5$	19.7	19.8
12	C_2H_5	$COCH_2Cl$	C_6H_6	180	65	$C_{14}H_{14}ClN_5O_5$	19.3	19.0
13	CH_3	CH_2OH	EtOH	154	90	$C_{12}H_{13}N_5O_5$	23.0	22.8
14	C_2H_5	CH_2OH	EtOH	219	85	$C_{13}H_{15}N_5O_5$	21.9	21.8
15	CH_3	Piperidinomethyl	EtOH	180	70	$C_{17}H_{22}N_6O_4$	22.3	22.4
16	CH_3	Morpholinomethyl	EtOH	191	65	$C_{16}H_{20}N_6O_5$	21.9	22.3
17	CH_3	$CH_2NHC_2H_5$	EtOH	143	60	$C_{14}H_{18}N_6O_4$	25.4	25.1
18	CH_3	$CH_2N(CH_3)_2$	EtOH	165	55	$C_{14}H_{18}N_6O_4$	25.1	25.1
19	CH_3	$CH_2N(C_2H_5)_2$	EtOH	161	60	$C_{16}H_{22}N_6O_4$	23.2	23.3
20	CH_3	$CH_2NHC_3H_7$-n	EtOH	184	70	$C_{15}H_{20}N_6O_4$	24.4	24.1
21	CH_3	$CH_2NHC_4H_9$-iso	EtOH	188	55	$C_{16}H_{22}N_6O_4$	22.9	23.3
22	CH_3	$CH_2N(CH_3)C_6H_5$	EtOH	142	60	$C_{19}H_{20}N_6O_4$	20.9	21.2
23	CH_3	$CH_2N(CH_2C_6H_5)_2$	EtOH	182	70	$C_{26}H_{26}N_6O_4$	17.3	17.3
24	C_2H_5	Piperidinomethyl	EtOH	167	65	$C_{18}H_{24}N_6O_4$	21.4	21.6
25	C_2H_5	Morpholinomethyl	EtOH	177	60	$C_{17}H_{22}N_6O_5$	21.6	21.5
26	C_2H_5	$CH_2NHC_2H_5$	EtOH	131	50	$C_{15}H_{20}N_6O_4$	24.3	24.1
27	C_2H_5	$CH_2N(CH_3)_2$	EtOH	170	55	$C_{15}H_{20}N_6O_4$	23.9	24.1
28	C_2H_5	$CH_2N(C_2H_5)_2$	EtOH	145	65	$C_{17}H_{24}N_6O_4$	21.9	22.3
29	C_2H_5	$CH_2NHC_3H_7$-n	EtOH	146	65	$C_{16}H_{22}N_6O_4$	23.3	23.3
30	C_2H_5	$CH_2NHC_4H_9$-iso	EtOH	187	60	$C_{17}H_{24}N_6O_4$	22.4	22.3
31	C_2H_5	$CH_2N(CH_3)C_6H_5$	EtOH	156	65	$C_{20}H_{22}N_6O_4$	20.4	20.5
32	C_2H_5	$CH_2N(CH_2C_6H_5)_2$	EtOH	192	75	$C_{27}H_{28}N_6O_4$	16.6	16.8
35	CH_3	H	EtOH	255	80	$C_{12}H_{13}N_5O_3$	25.3	25.5
36	CH_3	C_6H_5	EtOH	129	70	$C_{18}H_{17}N_5O_3$	20.1	19.9
37	CH_3	$SO_2C_6H_5$	EtOH	142	65	$C_{18}H_{17}N_5O_5S$	17.3	16.9
38	C_2H_5	H	EtOH	265	85	$C_{13}H_{15}N_5O_3$	23.9	24.2
39	C_2H_5	C_6H_5	EtOH	134	72	$C_{19}H_{19}N_5O_3$	19.3	19.2
40	C_2H_5	$SO_2C_6H_5$	EtOH	165	60	$C_{19}H_{19}N_5O_5S$	16.2	16.3

*Satisfactory C and H analyses were obtained for all the compounds.

in water (2 ml) and ethanol (5 ml). The reaction mixture was stirred further for 1.5 hr at room temperature and the product filtered, dried and crystallised from ethanol.

1: Yellow needles, m.p. 145°, Yield 95% (Found: C, 50.7; H, 4.7; N, 13.8. $C_{13}H_{15}N_3O_6$ requires C, 50.5; H, 4.9; N, 13.7%).

2: Pale yellow needles, m.p. 173°, Yield 98% (Found: C, 52.2; H, 5.1; N, 12.9. $C_{14}H_{17}N_3O_6$ requires C, 52.0; H, 5.3; N, 13.0%).

33: Yellow crystals, m.p. 154°, Yield 85% (Found: C, 52.0; H, 4.8; N, 14.9. $C_{12}H_{13}N_3O_5$ requires C, 51.6; H, 4.7; N, 15.1%).

34: Pale yellow fine needles, m.p. 160°, Yield 90% (Found: C, 52.9; H, 5.0; N, 14.6. $C_{13}H_{15}N_3O_5$ requires C, 53.2; H, 5.1; N, 14.3%).

4-Arylhydrazono-3-methyl-2-pyrazolin-5-ones (**3-8**) *and 4-arylazo-3,5-dimethyl-pyrazoles* (**35-40**) (*Table* 1)

A mixture of **1** (0.01 mol) and hydrazine hydrate (0.011 mol), phenylhydrazine or benzenesulphonhydrazide (0.01 mol) in ethanol (50 ml) was heated under reflux for 6 hr and left to cool. The solid obtained was filtered, dried and crystallized from an appropriate solvent to give **3**, **4** or **5**. The IR(KBr) spectrum of **4** displayed νC=O at 1730, νNH at 3390 and νC=N at 1950 cm^{-1}. A similar reaction of **2**, **33** and **34** with hydrazine hydrate, phenylhydrazine and benzenesulphonhydrazide gave **6-8**, **35-37** and **38-40** respectively.

The PMR spectral data of a few representative compounds are given below:

Table 2—Antiinflammatory Activity of the Compounds **3**, **4**, **5**, **6**, **7**, **8**, **9**, **14**, **23** and **35** in Albino Mice

Compd	Antiinflammatory activity*	
	Inhibition (%)	*P*
3	60.7	<0.01
4	05.6†	—
5	28.8	<0.20‡
6	50.3	<0.01
7	04.0†	—
8	45.9	<0.01
9	22.5	<0.20‡
14	58.2	<0.01
23	63.1	<0.01
35	06.0†	—

*Phenylbutazone (200 mg/kg), used as a reference drug, exhibited 65.1% ($P<0.01$) reduction in edema.
†Did not produce any reduction in paw edema weight when compared with the control group.
‡No significant difference from the control.

4: δ 2.2 (*s*, 3H, CH_3), 3.6 (*s*, 3H, OCH_3) and 7.4-8.2 (*m*, 8H, Ar – *H*).

35: δ 2.3 (*s*, 6H, 2 × CH_3), 3.7 (*s*, 3H, OCH_3) and 7.7 (*m*, 3H, Ar – *H*).

36: δ 2.3 (*s*, 6H, 2 × CH_3), 3.7 (*s*, 3H, OCH_3) and 7.6 (*m*, 8H, Ar – *H*).

37: Exhibited signals identical with those of compound **36**.

38: δ 1.5 (*t*, 3H, CH_3-CH_2O), 2.3 (*s*, 6H, 2 × CH_3), 4.1 (*q*, 2H, CH_3CH_2O) and 7.8 (*m*, 3H, Ar – *H*).

39: δ 7.6 (*m*, 8H, Ar – *H*) and the other signals which are identical with those of **38**.

Treatment of 4-alkoxy-2-nitrobenzene-diazonium chlorides with 3-methyl-2-pyrazolin-5-ones (**Ia**, **b**): *Formation of pyrazolones* (**3**, **4**, **6**, **7**)

A solution of 4-methoxy- or 4-ethoxy-2-nitroaniline (0.001 mol) in gl. acetic acid (2 ml) and conc. HCl (3 ml) was cooled and diazotized with sodium nitrite (0.069 g; 0.001 mol) in water (5 ml). The cold diazonium salt solution was slowly poured with stirring into a cold solution of Ia or Ib (0.001 mol), sodium hydroxide and sodium acetate in aq. ethanol. The mixture was left overnight and acidified with HCl. The precipitated product was found to be **3**, **4**, **6** or **7**. Its identity was established by direct comparison (m.m.p.) with that obtained above.

1-Acetyl-3-methyl-4-arylhydrazono-2-pyrazolin-5-ones (**9**, **10**; *Table* 1)

A suspension of **3** or **6** (1.0 g) and fused sodium acetate (1.0 g) in acetic anhydride (30 ml) was heated under reflux for 3 hr, cooled and poured into ice-cold water. After complete decomposition of excess acetic anhydride, the solid that separated out was filtered, dried and crystallized from an appropriate solvent to give **9** or **10**. The IR (KBr) spectrum of **10** displayed two $\nu C=O$ bands at 1710 and 1670 cm^{-1}. The PMR spectrum of **9** exhibited signals at δ 2.2 (*s*, 3H, CH_3), 2.6 (*s*, 3H, CH_3CO), 3.7 (*s*, 3H, OCH_3) and 7.7 (*m*, 3H, Ar – *H*).

4-Arylhydrazono-1-chloroacetyl-3-methyl-2-pyrazolin-5-ones (**11**, **12**, *Table* 1)

To a mixture of **3** or **6** (2.0 g) and chloroacetyl chloride (15 ml), was added ethanol and the reaction mixture heated under reflux on a steam-bath for 3 hr, left at room temperature overnight, and the separated solid filtered, dried and crystallized from an appropriate solvent to give **11** or **12**. The IR spectra exhibited two carbonyl bands at 1735 and 1680 cm^{-1}. The PMR spectrum of **11** displayed signals at δ 2.2 (*s*, 3H, CH_3), 3.5 (*s*, 2H, $COCH_2Cl$), 3.7 (*s*, 3H, OCH_3) and 7.7 (*m*, 3H, Ar – *H*).

Action of acetic anhydride on **11**: *Formation of* **9**

Compound **11** (0.5 g) was heated under reflux with acetic anhydride (15 ml) in the presence of a catalytic amount of fused sodium acetate (0.5 g) for 3 hr and poured into ice-water to give **9** (m.p. and m.m.p. 238°).

Action of pyridine on **11**: *Formation of* **3**

A mixture of **11** (0.5 g) and pyridine (20 ml) was heated under reflux for 3 hr and poured into water. The solid product was found to be **3** (m.p. and m.m.p. 260°).

4-Arylhydrazono-1-hydroxymethyl-3-methyl-2-pyrazolin-5-ones (**13**, **14**; *Table* 1)

To a suspension of **3** or **6** (1.0 g) in methanol (30 ml), was added formalin (10 ml) and the reaction mixture heated under reflux for 3 hr and set aside at room temperature overnight. The precipitated solid was filtered, dried and crystallized from an appropriate solvent to give **13** or **14**. The PMR of **13** exhibited signals at δ 2.2 (*s*, 3H, CH_3), 3.3 (*s*, 2H, NCH_2OH), 3.8 (*s*, 3H, OCH_3) and 7.2-8.0 (*m*, 3H, Ar – *H*). The PMR of **14** displayed signals at δ 1.4 (*t*, 3H, CH_3CH_2O), 2.35 (*s*, 3H, CH_3), 3.2 (br, *s*, 2H, NCH_2OH), 4.15 (*q*, 2H, CH_3CH_2O), 5.1 (*s*, 1H, OH) and 7.3-8.1 (*m*, 3H, Ar – *H*).

4-Arylhydrazono-3-methyl-1-(substituted aminomethyl)-2-pyrazolin-5-ones (**15-32**; *Table* 1)

To a mixture of **3** or **6** (0.01 mol) and an appropriate amine (0.02 mol) in methanol (50 ml), was added formalin (0.02 mol) and the mixture heated on a water-bath to ensure complete dissolution. The reaction

mixture was kept overnight at room temperature and the precipitated solid filtered, dried and crystallized from ethanol to give the corresponding Mannich base as orange crystals.

The PMR of some representative compounds are given below:

15: δ 1.53 (*m*, 6H, piperidine 3-, 4- and 5-methylene protons), 2.5 (*t*, 4H, piperidine 2- and 6-methylene protons), 2.15 (*s*, 3H, CH_3), 3.8 (*s*, 3H, OCH_3), 4.15 (*s*, 2H, $-NCH_2N-$) and 7.7 (*m*, 3H, Ar–*H*).

18: δ 2.2 (*s*, 3H, 3-CH_3), 3.2 [*s*, 6H, $N(CH_3)_2$], 3.6 (*s*, 3H, OCH_3), 4.1 (*s*, 2H, NCH_2N-) and 7.6 (*m*, 3H, Ar–*H*).

27: δ 1.5 (*t*, 3H, CH_3CH_2O), 2.2 (*s*, 3H, 3-CH_3), 3.1 [*s*, 6H, $N(CH_3)_2$], 4.0 (*s*, 3H, NCH_2N-), 4.2 (*q*, 2H, CH_3CH_2O) and 7.7 (*m*, 3H, ar-*H*).

Conversion of **13** *and* **14** *into* **15**, **16**, **23** *and* **24**

A mixture of **13** or **14** (0.5 g) and piperidine or morpholine (2 ml) was heated on a boiling water-bath for 3 hr. The oily residue was triturated with aq. ethanol and the solid product thus obtained was found to be identical (m.m.p.) with **15**, **16**, **23** or **24**.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1243-1244

Notes

A New Synthesis of (±)-Frontalin, the Pheromone of *Dendroctonus* Bark Beetles

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Received 24 *February* 1986; *accepted* 12 *May* 1986

3-Methyl-3-butenol(Ia) is converted into the corresponding iodide(Ic) via its tosylate (Ib). Alkylation of α-lithioacetone dimethylhydrazone with Ic followed by oxidative hydrolysis of the resulting hydrazone (II) with $NaIO_4$ results in the formation of 6-methyl-6-hepten-2-one (III) which on treatment with *m*-chloroperbenzoic acid gives the title compound (IV).

Frontalin[1], an aggregating pheromone isolated from the hindguts of the male western pine beetle has a unique bicyclic ketal structure 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (IV). Literature reports syntheses of both racemic[2] and optically active forms[3]. A straightforward and short synthesis of the title compound has been achieved (Scheme 1), which forms the subject of this note.

3-Methyl-3-butenol (Ia) was converted into corresponding iododerivative (Ic) via its tosylate (Ib). Alkylation[4] of α-lithioacetone dimethylhydrazone with Ic in tetrahydrofuran and HMPA as cosolvent at −78° led to 6-methyl-6-hepten-2-one dimethylhydrazone (II) in 73.8% yield. Oxidative hydrolysis[5] of II with aq sodium periodate in methanol at *p*H 7 and 20-25° resulted in the formation of 6-methyl-6-hepten-2-one (III) in 86% yield. The ketone was epoxidised[6] with *m*-chloroperbenzoic acid and the resulting crude epoxide distilled under reduced pressure to give (±) frontalin (IV), having IR and PMR spectral characteristics similar to those reported for a natural sample of IV.

Boiling points are uncorrected. IR spectra of thin films were recorded on a Perkin-Elmer spectrophotometer model 337 and PMR spectra in CCl_4 on a Varian EM-390 spectrometer using TMS as an internal standard. Silica gel G (ASC, Bombay) impregnated with calcium sulphate was used for TLC. The organic extracts were dried over anhydrous Na_2SO_4.

4-Iodo-2-methyl-1-butene (Ic)

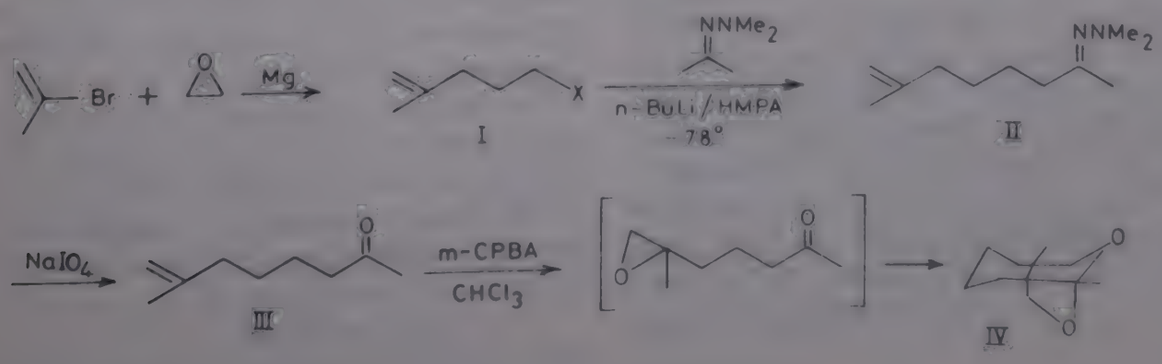
Compound (Ic) was prepared from 3-methyl-3-butenol (Ia) via its tosylate (Ib); IR: 1640 cm^{-1}; PMR (CCl_4): 4.73 (2H, *bs*, $H_2C=C<$), 3.16 (2H, *t*, $-CH_2I$), 2.5 (2H, *m*, $H_2C=\underset{|}{C}-CH_2$), 1.77 [3H, *s*, $H_2C=C(CH_3)-$].

6-Methyl-6-hepten-2-one dimethylhydrazone(II)

To a solution of acetone dimethylhydrazone (0.6 g, 6 mmol) in THF (10 ml) cooled to −78° under nitrogen was added a solution of *n*-BuLi in hexane (2 ml of 2.9*N*) followed by HMPA (1.5 ml) after 15 min. After stirring for 30 min more, Ic (0.98 g, 5 mmol) in THF (10 ml) was added and the reaction mixture was allowed to warm to room temperature and left overnight. After the addition of methanol (1 ml) followed by solvent removal by rotary evaporation *in vacuo*, the residue was dissolved in water, extracted with ether and dried. Removal of the solvent followed by distillation under reduced pressure led to the pure II, yield 0.62 g (73.8%); b.p. 60°/8-10 mm; IR: 1650 cm^{-1}; PMR(CCl_4): 4.70 (2H, *bs*, $H_2C=C<$), 2.3-1.86 [13H, *m*+*s*, $=NN(CH_3)_2$, $-CH_2-C-CH_3$, and $H_2C=C-CH_2$], 1.86-1.53 (5H, *m*+*s*, $-H_2C-CH_2-CH_2-$, $H_3C-\overset{CH_2}{\overset{\|}{C}}-$) (Found: C, 71.3; H, 11.8; N, 16.5. $C_{10}H_{20}N_2$ requires C, 71.4; H, 11.8; N, 16.6%).

6-Methyl-6-hepten-2-one (III)

Compound (II, 0.67 g, 4 mmol) was dissolved in methanol (60 ml) containing phosphate buffer (*p*H 7;



I, a: X = −OH
b: X = TOS
c: X = I

Scheme 1

3 ml). To this was added a solution of sodium periodate (2.2 eq) in water (15 ml) at 25° with stirring. Gas evolution and precipitation of sodium iodate ensued rapidly. After completion of hydrolysis (TLC monitoring), the reaction mixture was filtered, diluted with water, extracted with dichloromethane, dried and solvent evaporated. Distillation under reduced pressure gave pure (III, yield 0.430 g (86%); b.p. 45°/10 mm; IR: 1710 cm^{-1}; PMR(CCl_4): 4.75 (2H, *s*, $H_2C=\overset{1}{C}-$), 2.33 (4H, *t*, $H_2C=\overset{3}{C}-CH_2-H_2C-CO-$), 2.1 (3H, *s*, $-CO-CH_3$) 1.83-1.55 (5H, *m*+*s*, $H_3C-\overset{4}{C}-CH_2-CH_2-$) (Found: C, 76.1; H, 11.1. $C_8H_{14}O$ requires C, 76.2; H, 11.1%).

1,5-*Dimethyl*-6,8-*dioxabicyclo*[3.2.1]*octane* (*IV*)

A solution of *m*-chloroperbenzoic acid (2 g, 11.4 mmol) in $CHCl_3$ (30 ml) was added to an ice-cooled solution of III (1.1 g, 8 mmol) in $CHCl_3$ (20 ml). The mixture was left to stand overnight in a refrigerator, poured into aq sodium bicarbonate, extracted with $CHCl_3$ and dried. Removal of the solvent followed by distillation under reduced pressure gave compound IV, yield 0.57 g (52%); b.p. 45-48°/20 mm; IR: 2980, 1275, 1245, 1210, 1120, 1070, 1030, 935, 900, 870, 850 cm^{-1}; PMR(CCl_4): 3.40 (1H, *d*, B part of AB type *q*, J_{AB} = 7 Hz), 3.80 (1H, *d*, A part of AB type *q*, J_{AB} = 7 Hz), 1.5-1.8 [6H, *m*, $(CH_2)_3$], 1.40 (3H, *s*, 5-CH_3), 1.30 (3H, *s*, 1-CH_3) (Found: C, 67.5; H, 9.9. $C_8H_{14}O_2$ requires C, 67.6; H, 10.0%).

We are thankful to the UGC, New Delhi for financial support to one of us (SG).

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1245-1246

Occurrence of Two Rare Amides in *Medicago polymorpha*

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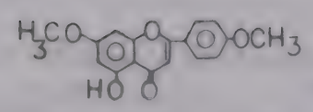
Received 28 *February* 1986; *accepted* 30 *April* 1986

A dipeptide alkaloid, aurantiamide acetate (II) and a phenylalanine derivative of rare occurrence, auranamide (III) along with 5-hydroxy-7,4′-dimethoxyflavone (I) have been isolated from the whole plant of *Medicago polymorpha* (Leguminosae). The occurrence of II and III and the flavone (I) in the genus *Medicago* is being reported for the first time.

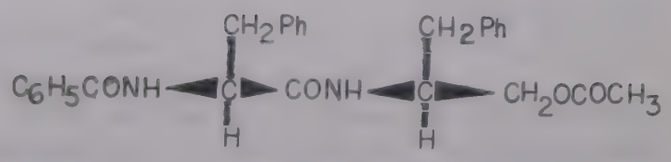
Plants belonging to the genus *Medicago* (fam: Leguminosae) elaborate several types of flavonoids[1-6] and steroids[7]. As a part of our programme on the screening of chemical constituents of plants of medicinal[8] importance, we have undertaken chemical investigation on *Medicago polymorpha*, which grows in the Western Himalayan region[9]. To the best of our knowledge ours is the first investigation on the chemical constituents of this species.

The pet. ether (b.p. 60°-80°) extract of the whole plant of *M. polymorpha* on chromatography over silica gel afforded a yellow crystalline solid from the benzene eluates, m.p. 168°, $C_{18}H_{18}O_4$; M^+ 298; UV(EtOH): 323, 340. It gave positive Shinoda test, indicating it to be a flavone. The compound exhibited IR bands at 3400 (−OH) and 1615 cm^{-1} (α,β-unsaturated ketone). It displayed in its PMR spectrum in $CDCl_3$ a six-proton singlet due to two methoxy groups at δ 3.88, a one-proton singlet due to phenolic OH at 12.8 (exchangeable with D_2O) and two doublets of one-proton each at 6.38 and 6.4 ($J = 3$ Hz) due to two *meta*-coupled aromatic protons. The peaks at δ 7.1 and 7.8 (2H each, *d*, $J = 10$ Hz) conformed to *AA′BB′* pattern. These spectral data together with the mass data [*m/z* 298 (M^+), 297, 269, 166 and 132 (RDA fragments)] have been found to be consistent with the known[10] 5-hydroxy-7,4′-dimethoxyflavone (I). Its identity was confirmed by direct comparison with an authentic sample. Interestingly, 5-oxygenated flavone (I) has never been encountered in the genus *Medicago* and this appears to be the first report of the occurrence of a 5-hydroxyflavone in the Leguminosae family.

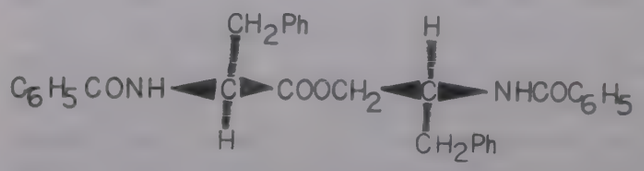
The benzene-ethyl acetate eluates obtained from the same chromatogram afforded successively compound-A and compound-B.



(I)



(II)



(III)

The compound-A, m.p. 184-85°, yield 0.003%, analysed for $C_{27}H_{28}N_2O_4$; M^+ 444; IR: 3320, 1660 (−CONH), 1602, 1580, 745, 695 (monosubstituted phenyl nucleus), 1725 and 1260 cm^{-1} (−$COCH_3$). Its UV, IR, PMR and particularly the mass spectral data compared well with those reported[11] for aurantiamide acetate (II). Its identity was further confirmed by direct comparison (m.m.p., co-TLC and IR) with an authentic sample.

Compound-B, m.p. 201-2° was obtained in extremely poor yield and it analysed for $C_{32}H_{30}N_2O_4$; M^+ 506 [IR: 3330, 1638 cm^{-1} (−CONH)]. It was identified as auranamide (III) by its spectral analysis and comparison (m.m.p., co-TLC, superimposable IR and PMR spectral data) with an authentic sample.

The occurrence of a dipeptide alkaloid (II) and a phenylalanine derivative (III) is of considerable chemotaxonomic significance as no other *Medicago* species have earlier been reported to elaborate such types of amides. We are currently investigating some *Medicago* species in search of biocidal compounds.

The authors are grateful to the CSIR, New Delhi, for the award of research fellowship to R.P. They also thank Prof. M. Silva, Universidad de concepcion, Chile and Dr A Banerji of Calcutta University, for the supply of authentic samples.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1247-1248

Studies in Terpenoids: Part LXXIII† – A One-step Synthesis of Emmotin-H

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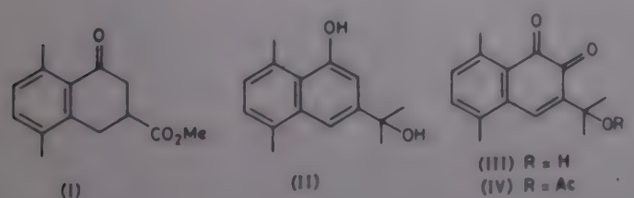
Received 21 *March* 1986; *accepted* 16 *May* 1986

In a one-step reaction iodoxybenzene converts the known 1-naphthol (II) to emmotin-H (III), a naturally occurring sesquiterpenic 1,2-naphthoquinone, in 50% yield. Depending on the reaction conditions, either III together with its acetate (IV) or only III have been isolated.

Following Barton's use of iodoxybenzene for the oxidation of 2-naphthol to 1,2-naphthoquinone[1], we treated several alkyl- and alkoxy-1-naphthols with this reagent and obtained the corresponding 1,2- along with the 1,4-naphthoquinones, when the 2- and 4-positions of the 1-naphthols were free[2]. The investigation[2] provided us a convenient route to mansonone-A[3,4], a naturally occurring sesquiterpenic tetrahydro-7,8-naphthoquinone. In the present note we describe a one-step synthesis of emmotin-H (III) based on iodoxybenzene oxidation.

The key reaction in an earlier multistep synthesis[5] of III, a sesquiterpenic 1,2-naphthoquinone isolated from the trunk wood of *Emmotum nitens*[6], was based on the selenium dioxide oxidation of the tetralone ester (I). The known sesquiterpenic 1-naphthol[7] (II), an isomer of naturally occurring emmotin-G[6], serves as the substrate in the present one-step synthesis of III.

Treatment of II with iodoxybenzene[8] in acetic acid furnished III in 40%, and the corresponding acetate (IV) as a minor product in 11% yield. In the oxidation a change in the medium from acetic acid to aq acetonitrile ($CH_3CN : H_2O$, 3:1) led to the isolation of III in 50% yield identical with the natural product[4,5] (IR and PMR). The convenient one-step transformation of a 1-naphthol to a 1,2-naphthoquinone in fair yield by codoxybenzene oxidation and the preservation of the labile benzylic tertiary hydroxyl of the compounds under study (II and III) are worthy of attention. Melting points are uncorrected. Petroleum ether refers to the fraction b.p. 60-80°.



(I) (II) (III) R = H (IV) R = Ac

3-(2-Hydroxyisopropyl)-5,8-dimethyl-1,2-naphthoquinone (Emmotin-H) (III): (A) By oxidation of II with iodoxybenzene in acetic acid

To the naphthol (II, 0.3 g) in gl acetic acid (3 ml) was added a slurry of iodoxybenzene[8] (0.4 g) in gl acetic acid (60 ml) under stirring at room temperature. After 3 min, water (200 m) was added and the product was extracted with ether (60 ml × 5). The ether extract was washed with saturated sodium bicarbonate and brine and dried (Na_2SO_4). Removal of the solvent, followed by preparative TLC (silica gel, chloroform) of the residue gave emmotin-H (III) (more polar) and its acetate(IV) (less polar). Emmotin-H(III) (128 mg, 40%), dark red crystals, m.p. 178-80° (ether-pet ether); IR (KBr): 3483, 1687, 1657, 1621, 1373, 1245, 1196, 1134 cm^{-1}; UV (EtOH): 218.4 ($\log\varepsilon$ 4.51), 254.6 (4.62), 432 nm (3.86); PMR ($CDCl_3$): δ 1.57 (6H, *s*, CH_3COHCH_3), 2.48 (3H, *s*, C_5-CH_3), 2.63 (3H, *s*, C_8-CH_3), 3.07 (1H, *b*, exchangeable with D_2O, OH), 7.15, 7.32 (2H, AB_q, $J=8$ Hz, C_6-H, C_7-H) and 7.83 (1H, *s*, C_4-H) (Found: C, 73.5; H, 7.0. Calc for $C_{15}H_{16}O_3$: C, 73.8; H, 6.6%).

Emmotin-H acetate (IV) (41 mg, 11%), orange red crystals, m.p. 113-15° (ether-pet ether); IR (nujol): 1743, 1689, 1673, 1628, 1377, 1262-1243 (broad), 1185, 1145 cm^{-1}; UV (EtOH): 220 ($\log\varepsilon$ 4.52), 255 (4.66), 425 nm (3.88); PMR ($CDCl_3$): δ 1.75 [6H, *s*, $C(CH_3)_2$], 2.06 (3H, *s*, $OCOCH_3$), 2.46 (3H, *s*, C_5-CH_3), 2.62 (3H, *s*, C_8-CH_3), 7.14, 7.31 (2H, AB_q, $J=8$ Hz, C_6-H, C_7-H) and 7.63 (1H, *s*, C_4-H) (Found: C, 70.9; H, 6.7. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%).

(B) By oxidation of II with iodoxybenzene in aqueous acetonitrile

A mixture containing II (200 mg), iodoxybenzene (500 mg), acetonitrile (15 ml) and water (5 ml) was stirred for 30 hr at room temperature. Ethers (75 ml) was added to the reaction mixture. After washing with brine (50 ml), the organic phase was dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue chromatographed over preparative TLC plates (silica gel, chloroform) to give emmotin-H (III) (110 mg, 51.8%) as the sole product, which was identical in all respects with III prepared by the procedure (A).

† For Part LXXII of the series, see ref. 2.

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The authors thank the UGC, New Delhi, for financial assistance to one of their (TPV) under Faculty Improvement Programme and the Dept of Atomic Energy, Bombay for the award of a senior research fellowship to DM.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1249-1250

Synthesis of Norphytene & Its Isomer 2,6,10,14-Tetramethyl-pentadec-2-ene†

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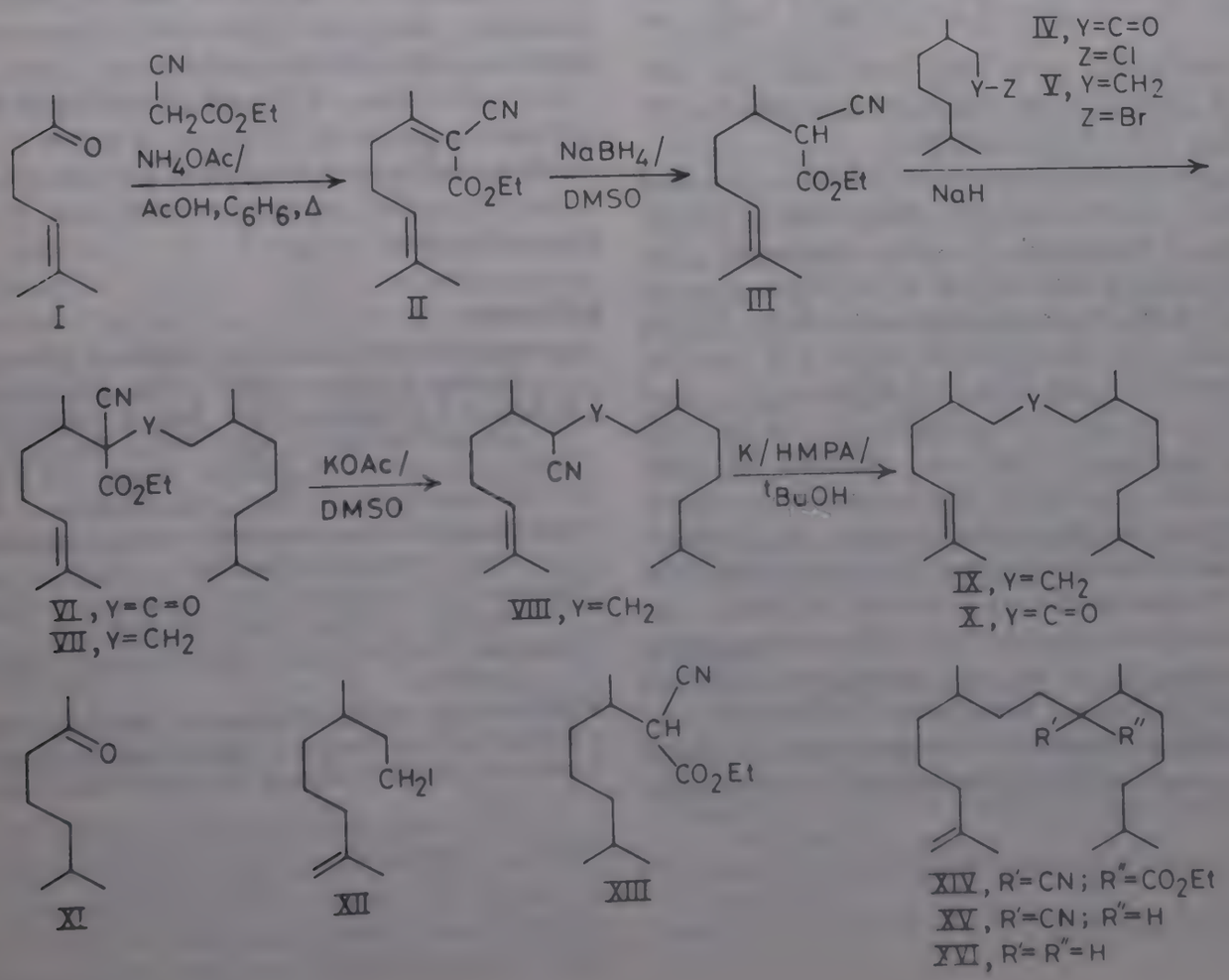
Received 28 *February* 1986; *accepted* 12 *May* 1986

Norphytene (XVI) has been synthesised employing methylheptanone (XI) and rhodinyl iodide (XII) as the eight-carbon and ten-carbon units respectively, with ethyl cyanoacetate providing the one-carbon bridge between these two units. Similarly the isomer of norphytene, 2,6,10,14-tetramethylpentadec-2-ene (IX) has been obtained from methylheptanone (I) (8-carbon unit), dihydrocitronellylbromide (V) (10-carbon unit) and ethyl cyanoacetate (one-carbon bridge).

In continuation of our earlier work[1] on the synthesis of the title hydrocarbons (IX, XVI), in the present synthesis of IX and XVI we have employed ethyl cyanoacetate as one-carbon unit to bridge the two chains consisting of eight and ten carbons respectively. The hydrocarbons have already been converted into phytol and phytone[2] and these are important intermediates for the synthesis of vitamin E.

Condensation of methylheptanone (I) with ethyl cyanoacetate using $NH_4OAc/AcOH$ in refluxing benzene led to 3,7-dimethyl-2-cyano-oct-2,6-dienoic acid ethyl ester (II) in 75% yield[3]. II was selectively reduced with $NaBH_4$ in DMSO to give 3,7-dimethyl-2-cyanooct-6-enoic acid ester (III) in 86% yield; b.p. 100°/5 mm; IR(film): 2240 (−CN), 1760 (−CO_2Et) cm^{-1}; PMR(CCl_4): δ 1.05, 1.11 (2*d*, 3H, $CH_3-\overset{|}{C}H-$, $J=6$ Hz, diastereomers), 1.3, (*t*, 3H, CH_3-CH_2-OCO, $J=7$ Hz), 1.6, 1.66 [2*s*, 6H, $=C(CH_3)_2$], 3.41 [*dd*, 1H, $-CH(CN)(CO_2Et)$, $J=5$ Hz], 4.21 (*q*, 2H, CH_3-CH_2-OCO, $J=7$ Hz), 5.00 (*bt*, 1H, olefinic proton).

Base-catalysed acylation of III (NaH in benzene) by 3,7-dimethyloctanoyl chloride (IV) led to 2,6,10,14-tetramethyl-7-cyano-7-carbethoxy-8-oxo-pentadec-2-ene (VI) in 64% yield; IR(film): 2230 (−CN), 1766 (CO_2Et), 1730 ($\succ C=O$) cm^{-1}; PMR(CCl_4): δ 0.86 (*d*,



†NCL Communication No. 4011

12H, $4CH_3-CH-$, $J=6$ Hz), 1.58, 1.66 [2*s*, 6H, $=C(CH_3)_2$], 2.53, 2.63 (2*m*, 3H, $CH(CN)(CO_2Et)COCH_2$), 4.18 [*q*, 2H, CH_3-CH_2-OCO, $J=7$ Hz), 5.00 (*bt*, 1H, olefinic proton); M^+ 377.

Attempts to obtain 2,6,10,14-tetramethylpentadec-2-ene-8-one (X) by hydrolysis/decarboxylation sequence and consequently IX therefrom by reduction were unsuccessful.

In the alternate approach to obtain IX, the cyanoacetate (III) was subjected to base-catalysed (NaH in benzene-HMPA, 9:1) alkylation with dihydrocitronellyl bromide (V) when 2,6,10,14-tetramethyl-7-cyano-7-carbethoxypentadec-2-ene (VII) was obtained in 50% yield; MS: *m/z* 363 (M^+); IR(film): 2230 ($-CN$), 1738 ($-CO_2Et$) cm^{-1}; PMR(CCl_4): δ 0.85 (*d*, 9H, $3\times CH_3-CH-$, $J=6$ Hz), 1.03 [*d*, 3H, $CH_3-CH-C(CN)-CO_2Et$, $J=6$ Hz], 1.33 (*t*, 3H, CH_3CH_2-OCO, $J=7$ Hz), 1.6, 1.66 [2*s*, 6H, $=C(CH_3)_2$], 4.33 (*q*, 2H, CH_3-CH_2-OCO, $J=7$ Hz), 5.03 (*bt*, 1H, olefinic proton).

Heating VII in DMSO at 150° in the presence of potassium acetate for 4 hr[4] furnished the decarboethoxylated compound, 2,6,10,14-tetramethyl-7-cyano-pentadec-2-ene (VIII) in 90% yield; IR(film): 2225 ($-CN$) cm^{-1}; PMR(CCl_4): δ 0.8 (*d*, 9H, CH_3-CH-, $J=6$ Hz), 1.0 [*d*, 3H, $CH_3-CH-C(CN)(CO_2Et)$, $J=6$ Hz] 1.56, 1.63 [2*s*, 6H, $=C(CH_3)_2$], 5.0 (*bt*, 1H, olefinic proton); MS: *m/z* 291 (M^+); b.p. 170-72° (bath)/4 mm.

Compound (VIII) in equimolar *t*-BuOH was added dropwise to a stirred solution of potassium in HMPA (2 g atm of metal/mol of cyano compound)[5]. The reaction mixture was worked-up in 1 hr to give the desired 2,6,10,14-tetramethylpentadec-2-ene (IX) in 76% yield; b.p. 125-27° (bath)/1 mm; MS: *m/z* 266 (M^+); PMR(CCl_4): δ 0.85 (*d*, 12H, $4CH_3-CH-$, $J=6$ Hz), 1.6, 1.66 (2*s*, 6H, $=C(CH_3)_2$], 5.06 (*bt*, 1H, olefinic proton). It (IX) was identical with the hydrocarbon reported in the literature[1a]. Similarly 2,6,10,14-tetramethylpentadec-1-ene (norphytene) (XVI) was prepared following the above strategy but using 3,7-dimethyl-2-cyanooctanoic acid ethyl ester (XIII) and rhodinyl iodide (XII). XIII was obtained by condensation of XI and ethyl cyanoacetate followed by $NaBH_4$ reduction. Alkylation of XIII by rhodinyl iodide (XII) afforded XIV. The yields obtained for all the steps were similar to those obtained in the synthesis of IX above. The spectral data and physical constants of all the intermediates and the final compounds are given below:

3,7-Dimethyl-2-cyanooctanoic acid ethyl ester (XIII): IR(film): 2235 ($-CN$), 1760 (CO_2Et) cm^{-1}; PMR(CCl_4): δ 0.85 (*d*, 6H, $2\ CH_3-CH-$, $J=6$ Hz), 1.05, 1.1 (isomers 2*d*, 3H, CH_3-CH-, $J=6$ Hz), 1.3 (*t*, 3H, CH_3-CH_2-OCO, $J=7$ Hz), 3.4 [*dd*, 1H, $-CH(CN)(CO_2Et)$, $J=5$ Hz], 4.2 (*q*, 2H, CH_3-CH_2-OCO, $J=3$ Hz); b.p. 105-7°/5 mm.

2,6,10,14-Tetramethyl-7-cyano-7-carbethoxy-pentadec-1-ene (XIV): IR(film): 2230 ($-CN$), 1742 ($-CO_2Et$) 1648, 885 (exomethylene) cm^{-1}; PMR(CCl_4): δ 0.83 (*d*, 9H, $3\ CH_3-CH-$, $J=6$ Hz), 1.68 (*s*, 3H, $>C-CH_3$), 4.25 (*q*, 2H, CH_3-CH_2-OCO, $J=7$ Hz), 4.6 (*bs*, 2H, $>C=CH_2$); MS: *m/z* 363 (M^+).

2,6,10,14-Tetramethyl-7-cyano-pentadec-1-ene (XV): IR(film): 2223 ($-CN$), 1645, 885 (exomethylene) cm^{-1}; PMR(CCl_4): δ 0.83 (*d*, 9H, $3\ CH_3-CH-$, $J=6$ Hz), 1.0 (*d*, 3H, CH_3-CH-; $J=6$ Hz), 1.68 (*s*, 3H, $>C-CH_3$), 2.43 (*m*, 1H, $-CH-CN$), 4.6 (*bs*, 2H, $>C=CH_2$); MS: *m/z* 291 (M^+); b.p. 149-51°/2 mm.

Norphytene (XVI): IR(film) 1640, 890 (exomethylene) cm^{-1}; PMR($CDCl_3$): δ 0.80 (*d*, 12H, $4\ CH_3-CH-$, $J=6$ Hz), 1.66 (*s*, 3H, $>C-CH_3$) 4.6 (*bs*, 2H, $>C=CH_2$); MS: *m/z* 266 (M^+), b.p. 125-27° (bath)/1 mm (lit. 110°/0.3 mm)[6].

The hydrocarbon (XVI) was identical with the one obtained by pyrolysis[6] of vitamin E at 400°C.

All the boiling points reported are uncorrected.

One of us (ASP) thanks the CSIR, New Delhi for financial support.

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Indian Journal of Chemistry
Vol. 25B, December 1986, p. 1251

Structural Confirmation of Eriodictyol 7-Methyl Ether, a New Flavanone Occurring in *Wyethia glabra* Nutt

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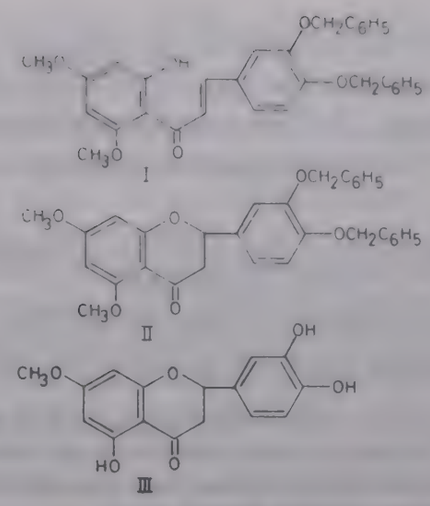
Received 28 *April* 1986; *accepted* 10 *June* 1986

5,3',4'-Trihydroxy-7-methoxyflavanone (III), isolated from *Wyethia glabra* Nutt. [*Phytochemistry*, **24** (1985) 1614], designated as eriodictyol 7-methyl ether, has been synthesised by the cyclization of 3,4-dibenzyloxy-2'-hydroxy-4',6'-dimethoxychalkone (I), followed by concerted debenzylation and partial demethylation of the resulting flavanone using anhydrous $AlCl_3$ in acetonitrile.

McCormick *et al*[1] isolated a number of compounds from *Wyethia glabra* Nutt[2]. These authors considered one of them to be eriodictyol 7-methyl ether [5,3',4'-trihydroxy-7-methoxyflavanone (III)] on the basis of spectral data. The present note describes the synthesis of III by cyclization[3] of 3,4-dibenzyloxy-2'-hydroxy-4',6'-dimethoxychalkone (I) to the flavanone (II). Concerted debenzylation and partial demethylation of II using aluminium chloride in acetonitrile[4] furnished the desired III.



3,4-Dibenzyloxy-2'-hydroxy-4',6'-dimethoxychalkone (I)

A solution of 2-hydroxy-4,6-dimethoxyacetophenone[5] (2 g) and 3,4-dibenzyloxybenzaldehyde (3 g) in ethanol (30 ml) was treated with potassium hydroxide (3 g in 30 ml) and kept at room temperature for 48 hr. Usual work-up afforded (I), which crystallised from ethyl acetate-light petroleum as yellowish orange needles (2.4 g), m.p. 153-54° (Found: C, 74.9; H, 5.6. $C_{31}H_{28}O_6$ requires C, 75.0; H, 5.6%). It gave brown colouration with ethanolic ferric chloride; PMR ($CDCl_3$/TMS): δ 3.77 (3H, *s*, $-OCH_3$), 3.80 (3H, *s*, $-OCH_3$), 5.18 (4H, *s*, $2\times -OCH_2C_6H_5$), 6.05 (1H, *s*, C_3-H), 6.92 (1H, *d*, $J=9$Hz, C_5-H), 7.25-7.50 (14H, *m*, C_2-H, C_6-H, $C_{2'}-H$, $C_{5'}-H$, & $2\times -OCH_2C_6H_5$), 7.68 (1H, *d*, $J=17$Hz, $C_\beta-H$) 13.02 (1H, *s*, OH).

3',4'-Dibenzyloxy-5,7-dimethoxyflavanone (II)

A solution of I (2 g) in methanolic sulphuric acid (30 ml; 4%) was refluxed for 10 hr. Usual work-up gave II as a colourless solid which crystallised from ethanol as colourless needles (1.5 g), m.p. 72-74° (Found: C, 74.9; H, 5.6. $C_{31}H_{28}O_6$ requires C, 75.0; H, 5.64%). It did not give any colour with ethanolic ferric chloride; PMR ($CDCl_3$/TMS): δ 2.61 (1H, *dd*, $J=16$ Hz, C_3-H), 3.82 (3H, *s*, $-OCH_3$), 3.86 (3H, *s*, $-OCH_3$), 5.15 (4H, *s*, $2\times -OCH_2C_6H_5$) 5.45 (1H, *dd*, $J=12$ Hz, C_2-H), 5.92 (1H, *s*, C_6-H), 7.20 (1H, *d*, $J=8.5$ Hz, $C_{5'}-H$), 7.40 (12H, *m*, $C_{2'}-H$, $C_{6'}-H$ and $2\times -OCH_2C_6H_5$).

5,3',4'-Trihydroxy-7-methoxyflavanone (III)

Compound (II, 0.3 g) was dissolved in anhydrous acetonitrile (35 ml) and treated with anhydrous aluminium chloride (0.35 g) and then refluxed for 4 hr. Usual work-up of the reaction mixture gave the desired flavanone (III) (0.15 g). It gave olive-green colouration with ethanolic ferric chloride; PMR ($CDCl_3$/TMS): δ 2.40 (1H, *d*, $J=16$Hz, C_3-H), 3.60 (3H, *s*, $-OCH_3$), 5.70 (1H, *dd*, $J=12$Hz, C_2-H), 5.98 (1H, *s*, C_6-H), 6.10 (1H, *s*, C_8-H), 7.22 (3H, *m*, $C_{2'}-H$, $C_{5'}-H$ and $C_{6'}-H$), 13.98 (3H, *s*, $-OH$); UV (MeOH): 280, 322 (sh); $+AlCl_3$: 302; $+HCl$: 300; 364 (sh) nm.

My grateful thanks are due to Prof N R Bannerjee for his constant encouragement.

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Indian Journal of Chemistry
Vol. 25B, December 1986, p. 1252

Dehydrogenation of Dihydrofuranocoumarins to Furanocoumarins Using 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)

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Received 5 *March* 1986; *accepted* 21 *May* 1986

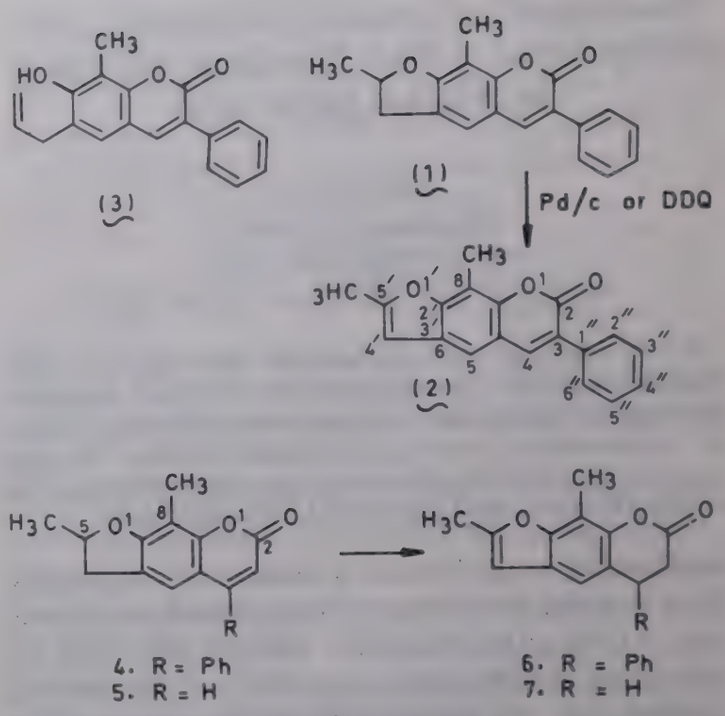
Dehydrogenation of dihydrofuranocoumarins (**1**, **4**, **5**) has been successfully carried out using DDQ and the corresponding furanocoumarins (**2**, **6**, **7**) obtained have been characterised by elemental analyses and PMR spectral data.

Ortho-hydroxyallylcoumarins are being increasingly used in recent times as starting materials for the synthesis of naturally occurring 2-substituted[1] furanocoumarins as well as unsubstituted[2] furanocoumarins. Further, these coumarins are photodynamically active and are knwon to have marked physiological[3,4] action.

2-Substituted furanocoumarins are usually obtained by the cyclization of *ortho*-hydroxyallylcoumarins, followed by dehydrogenation over Pd/C of the formed dihydrofuranocoumarins. No other reagent appears to have been reported so far for dehydrogenation of these coumarins. Herein we report the use of DDQ, as a versatile reagent for the conversion of 2-methyl-2,3-dihydrofuranocoumarins to corresponding furanocoumarins. Although DDQ has been used in the case of simple dihydrofuranocoumarins[5], its use in the conversion of 2-methyldihydrofuranocoumarins was not thought of possible due to the presence of 2-methyl substituent which may be oxidized to aldehyde group.

As a first exaple 4',5'-dihydro-5',8-dimethyl-3-phenylpsoralene (**1**) was dehydrogenated with DDQ in benzene to give 5',8-dimethyl-3-phenylpsoralene (**2**), identical with the sample obtained by dehydrogenation of **1** with Pd/C in diphenyl ether. The starting **1** which is being reported for the first time was prepared (i) by the cyclization of 6-allyl-7-hydroxy-8-methyl-3-phenylcoumarin (**3**) with the sulphuric acid and (ii) by Claisen rearrangement of 7-allyloxy-8-methyl-3-phenylcoumarin.

Similarly dehydrogenation of 4',5'-dihydro-5',8-dimethyl-4-phenylpsoralene[6] (**4**) and 4',5'-dihydro-5',8-dimethylpsoralene[6] (**5**) afforded compounds **6** and **7** respectively.



Dehydrogenation of dihydrofuranocoumarin (**1**) *to furanocoumarin* (**2**): *General procedure*

Compound (**1**, 1 g) in anhydrous benzene (10 ml) was refluxed for 40 hr with DDQ (80 mg). The solution was filtered, the filtrate washed successively with aq. sodium bicarbonate (10%) and water, dried ($MgSO_4$) and distilled to give a residue. The residue, on column chromatography over silica gel and elution with benzene give **2** which crystallized from methanol to give yellow needles (80%), m.p. 112-13° (Found C, 78.6; H, 4.8. $C_{19}H_{14}O_3$ requires C, 78.7; H, 4.7%); PMR ($CDCl_3$): δ 2.46 and 2.66 (each *s*, each 3H, 2 × $-CH_3$), 6.27 (*s*, 1H, H-3), 7.16-7.41 (*m*, 4H, H-4', H-3'', H-4'', H-5''), 7.56 (*m*, 2H, H-2', H-6'', and 7.75 (*s*, 1H, H-4).

Similarly **6** and **7** were prepared by the dehydrogenation of 5',8-dimethyl-4',5'-dihydro-4-phenylpsoralene[6] (**4**) and 5',8-dimethyl-4',5'-dihydropsoralene[6] (**5**) with DDQ [**6**: m.p. 170° (lit.[6], m.p. 170°); **7**: m.p. 176-77° (lit[6]. m.p. 176°)].

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1253-1254

Cleavage of Aryl Benzyl Ethers by Heterogeneous Catalytic Transfer Hydrogenation

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Received 28 *February* 1986; *accepted* 29 *May* 1986

Aryl benzyl ethers are effectively debenzylated under heterogeneous catalytic transfer hydrogenation using Pd/C as catalyst and formic acid or its salts (sodium formate, ammonium formate and triethylammonium formate) as hydrogen donors. The method is illustrated with several examples from phenolic natural products.

A variety of methods is available in organic synthesis for the protection and deprotection of hydroxyl functionality and the subject has been reviewed[1]. Hydrogenolysis of benzyl ethers by catalytic transfer hydrogenation (CTH)[2] is increasingly finding applications in recent years. The applications of palladium catalysed debenzylations by CTH using such hydrogen donors as cyclohexene[2b], hydrazine[2], 1,4-cyclohexadiene[2b], formic acid[2b], ammonium formate[2b,3], 2-propanol[2b] have so far been in the areas of N-benzyl(peptides), alkyl-O-benzyl(serine, threonine and sugars), benzyl esters (amino acids, peptides) etc. Although in principle, aryl benzyl ethers also should cleave readily, to the best of our knowledge, application of CTH procedures to aryl benzyl ethers has not been described, except in the case of tyrosine. The use of sodium ethoxide as a hydrogen donor[14] is a recent addition to CTH methods and has found application in the debenzylation of phenyl benzyl ether and 2-pyridyl benzyl ether. It is the purpose of this note to report our findings on the use of sodium formate-formic acid-Pd/C-methanol system (method A) and Et_3N-HCOOH-Pd/C system (method B) in CTH for debenzylation phenyl benzyl ethers, especially phenolic natural products.

Initial experiments showed that 2-naphthol benzyl ether was cleaved readily to 2-naphthol using the commercially available Pd/C (10% or 5%) and cyclohexene, formic acid, sodium formate and hydrazine as hydrogen donors; 2-propanol was ineffective. In subsequent experiments sodium formate-formic acid-Pd/C-methanol (method-A) and Et_3N-HCOOH-Pd/C system[5] (method-B, Heck's system) were chosen from the point of view of their simplicity, mild conditions and convenience. Debenzylation by method-A was very slow at room temperature and reasonably fast at the boiling point of methanol. Similar results were obtained using ammonium formate-Pd/C-methanol system[3]. On the other hand method-B brought about debenzylation in relatively short time at room temperature (Reductions

Table 1—Debenzylation of Aryl Benzyl Ethers with Sodium Formate-Formic Acid-Pd/C (Method-A) and Et_3NH^+ $HCOO^-$-Pd/C (Method-B)

Sl. No.	Substrate	Product	Yield (%)	
			Method A[a] (time)	Method B[b] (time)
1.	2-Naphthyl benzyl ether	2-Naphthol	79 (0.5 hr)	95 (10 min)
2.	4-Benzyloxy-2-hydroxyacetophenone	2,4-Dihydroxyacetophenone	90 (1 hr)	—
3.	4-Benzyloxybenzoic acid	4-Hydroxybenzoic acid	75 (10 min)	85 (1 hr)
4.	7-Benzyloxy-4-methylcoumarin	7-Hydroxy-4-methylcoumarin	92 (1.5 hr)	90 (1.5 hr)
5.	4-Benzyloxy-3-methoxybenzaldehyde	4-Hydroxy-3-methoxybenzaldehyde	92 (4 hr)	90 (1.5 hr)
6.	4-Benzyloxy-3-methoxyallylbenzene	4-Hydroxy-3-methoxy-n-propylbenzene	90 (4 hr)	—
7.	4,4'-Dibenzyloxy-2'-hydroxychalcone	2',4',4-Trihydroxydihydrochalcone	75 (4 hr)	80 (1.5 hr)
8.	4-Benzyloxyvanillylidenacetone	Dihydrovanillylidenacetone	90 (4 hr)	85 (1.5 hr)
9.	5-Hydroxy-7-benzyloxyflavone	5,7-Dihydroxyflavone	90 (2 hr)	—
10.	7-Benzyloxyisoflavone	7-Hydroxyisoflavanone	54 (2 hr)	—
11.	Myricanol dibenzyl ether	Myricanol[6]	80 (3 hr)	—
12	4-Benzyloxy-3-methoxy-hydrocinnamic acid	4-Hydroxy-3-methoxyhydrocinnamic acid	—	93 (1 hr)
13.	2-Hydroxy-4,6-dibenzyloxyacetophenone	2,4,6-Trihydroxyacetophenone	—	75 (2 hr)

(a) Reflux; and (b) room temperature.

using Heck's system[5] are generally carried out at 100°C for several hours). Table 1 lists several types of aryl benzyl ethers which have been subjected to these procedures.

These methods are useful in the case of phenolic aldehydes and ketones, since the carbonyl group is not reduced appreciably unlike in catalytic hydrogenation. In flavonoids the 2,3-double bond is resistant to hydrogenation except in the case of isoflavones where partial reduction is observed.

Debenzylation of aryl benzyl ethers by CTH with formic acid or its salts is of preparative value and operationally simple and convenient. This system is far more superior than EtOH-$NaOC_2H_5$-Pd/C method[4] in which the medium is alkaline. Benzyl ether cleavage with Et_3N-HCOOH-Pd/C is a new application of this system[5].

Pd/C (10%) was obtained from Arora-Matthey, Calcutta. methanol was of LR grade. Sodium formate was prepared by the neutralisation of sodium hydrogen carbonate with formic acid and stored in a desiccator. Et_3N was dried (NaOH) and distilled. Formic acid (99%) was a BDH product. The aryl benzyl ethers were prepared using standard methods. Some of them are available in our laboratory.

Method A

A solution containing aryl benzyl ether (1 mmole), methanol or ethanol (60 ml), Pd/C (10%, 0.2 mmol Pd), formic acid (4 mmol) and sodium formate (1 mmol) was refluxed for time periods mentioned in Table 1. After the reaction was over (TLC monitoring), the catalyst was filtered off, the filtrate concentrated and the product isolated in the usual way.

The presence of sodium formate is known[7] to accelerate the palladium catalysed reduction by formic acid.

Method B

Debenzylation was carried out employing essentially the same procedure as described by Cortese and Heck[5], except that reactions were carried out at room temperature for about 1.5 hr.

We thank the CSIR, New Delhi for financial support.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1255-1257

Action of Grignard Reagents on 2-(N-Arylcarboxamido)-3(*H*)-oxonaphtho[2,1-*b*]pyrans

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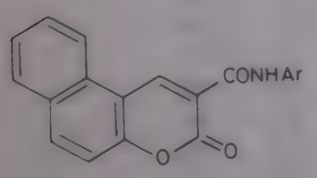
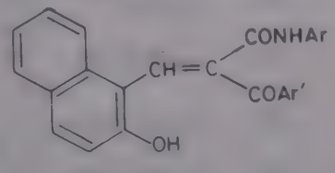
Received 22 *October* 1985; *revised and accepted* 13 *May* 1986

2-(N-Arylcarboxamido)-3(*H*)-oxonaphtho[2,1-*b*]pyran (I) reacts with Grignard reagents to give 1,2- and 1,4- addition products of the types 2-arylcarboxamido-2-benzoyl-1-(β-hydroxy-α-naphthyl)ethylenes (II) and 1-alkyl-2-(N-aryl-carboxamido)-1,2-dihydro-3(*H*)-oxonaphtho[2,1-*b*]pyrans (III). Their structures have been assigned by elemental analyses and spectral data (IR, PMR, mass).

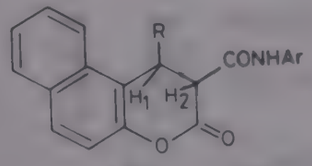
Several studies[1-5] are reported on the reaction of Grignard reagents with ethyl coumarin-3-carboxylate, 3-(N-arylamido)coumarin and ethyl benzocoumarin-3-carboxylate and in most cases 1,2- and 1,4- addition products are isolated. In the present investigation 2-(N-arylcarboxamido)-3(*H*)-oxonaphtho[2,1-*b*]pyrans (I) have been reacted with different Grignard reagents to give 1,2- and 1,4- addition products (II and III).



(I)



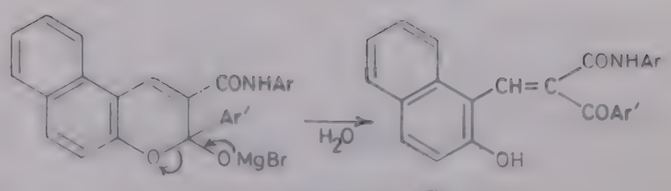
(II)



(III)

The required 2-carboxamidonaphthopyrans (Ia-c) were obtained by the direct interaction of ethyl 3(*H*)-oxonaphtho[2,1-*b*]pyran-2-carboxylate with different amines[6]. The interaction of I with excess arylmagnesium bromides in dry benzene furnished 2-arylcarboxamido-2-benzoyl-1-(β-hydroxy-α-naphthyl)ethylenes (IIa-d) as the only isolable products (Table 1).

The IR spectra of IIa-d exhibited bands at 1678 and 1728 due to C=O function[7] and a broad band at 3380-3200 cm^{-1} region due to OH and NH groups. The PMR spectrum of IIa displayed signals at δ 4.46 (*s*, 1H, NH, exchangeable with D_2O)[8], 5.6 (*s*, 1H, olefinic H), 7.33-7.9 (*m*, 16H, Ar−*H*) and 10.56 (*s*, 1H, OH, exchangeable with D_2O). In addition to these signals there appeared a very sharp singlet at δ 2.2 assignable to the methyl protons of the tolyl moiety in the case of compound IIc. The mass spectrum of IIa showed a molecular ion peak at *m/z* 393 (53%) together with a base peak at *m/z* 273 (100%); other significant peaks appeared at *m/z* 393 (5%), 316 (44), 299 (70), 273 (100), 231 (65), 215 (68), 197 (56), 168 (13), 138 (40) and 115 (40).



(II)

Scheme 1

It is presumed that 1,2- addition of phenylmagnesium bromide or anisylmagnesium bromide to the carbonyl group of the pyran ring gives a complex which rearranges as shown in Scheme1 to give II.

It is interesting to note that the interaction of alkylmagnesium halides with I affords 1-alkyl-2-(N-arylcarboxamido)-1,2-dihydro-3-(*H*)-oxonaphtho[2,1-*b*]pyrans (IIIa-p) as the only isolable products (Table 1).

The IR spectra of IIIa exhibited bands at 3270 (NH), 2950 (aliph. CH), 1650 and 1760 (C=O) and 1160 and 1240 cm^{-1} (C−O−C). The PMR of IIIh showed a well resolved triplet and quintet at δ 0.88-1.15 and 1.6-2.3 assignable to the methyl and the methylene protons respectively of the ethyl group attached to the pyran ring at position-4 (position-1 of III). The spin-spin coupling constants of these two types of protons were found to be 7.35 and 6 Hz, respectively. On the other hand the methyl protons of tolyl moiety were shifted downfield and appeared as a very sharp singlet at δ 2.2. The amide proton appeared as a broad singlet at δ 9.45 which was obscured by D_2O. The ten aromatic protons a set of signals between δ 7.6 and 8.3 and the pyran methine protons H-1 and H-2 as a quartet and a doublet at δ 4.25 and 4.4 respectively. In compounds III, H-1 and H-2 were found to have oxial and equatorial conformations respectively ($J_{H_1H_2} = J_{H_2H_1} = 1$ Hz).

The above findings show that compounds III were formed by the 1,4- addition of Grignard reagents to the conjugated double bond in the pyrone moiety of I, in full agreement with the results obtained by Decoret *et al.*[9] in the reaction of coumarin and by Islam *et al.*[5,10]

Table I – Characterization Data of 2-Arylcarboxamido-2-benzoyl-(β-hydroxy-α-naphthyl)ethylenes (IIa-d) and 2-(N-Arylcarboxamido)-1-alkyl-1,2-dihydro-3(*H*)-oxonaphtho[2,1-*b*]pyrans (IIIa-p)

Compd*	Ar	Ar'	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.)		
						C	H	N
IIa	C_6H_5	C_6H_5	215	60	$C_{26}H_{19}O_3N$	79.9 (79.4	6.0 4.8	3.5 3.6)
IIb	C_6H_5	$C_6H_4.OCH_3$-*p*	200	45	$C_{27}H_{21}O_4N$	76.2 (76.6	4.8 5.0	3.0 3.3)
IIc	$C_6H_4CH_3$-*p*	C_6H_5	204	60	$C_{27}H_{21}O_3N$	79.3 (79.6	5.1 5.2	3.3 3.4)
IId	$C_6H_4-OCH_3$-*p*	C_6H_5	210	55	$C_{27}H_{21}O_4N$	76.4 (76.6	4.8 5.0	3.2 3.3)
IIIa	C_6H_5	C_2H_5	180	50	$C_{22}H_{19}O_3N$	76.0 (76.5	5.4 5.5	4.0 4.1)
IIIb	C_6H_5	C_3H_7-*n*	163	60	$C_{23}H_{21}O_3N$	76.8 (76.9	6.2 5.9	4.2 3.9)
IIIc	C_6H_5	C_3H_7-iso	181	65	$C_{23}H_{21}O_3N$	76.8 (76.9	6.4 5.9	3.8 3.9)
IIId	C_6H_5	$CH_2CH=CH_2$	148	55	$C_{23}H_{19}O_3N$	77.2 (77.3	5.1 5.3	3.8 3.9)
IIIe	C_6H_5	C_4H_9-n	173	70	$C_{24}H_{23}O_3N$	77.0 (77.2	5.9 6.2	3.6 3.7)
IIIf	C_6H_5	C_4H_9-sec.	180	70	$C_{24}H_{23}O_3N$	77.0 (77.2	6.0 6.2	3.6 3.8)
IIIg	$C_6H_4.CH_3$-*p*	CH_3	168	50	$C_{22}H_{19}O_3N$	76.7 (76.5	5.6 5.5	4.0 4.1)
IIIh	$C_6H_4.CH_3$-*p*	C_2H_5	175	60	$C_{23}H_{21}O_3N$	76.2 (76.9	5.4 5.9	3.4 3.9)
IIIi	$C_6H_4.CH_3$-*p*	C_3H_7-*n*	160	65	$C_{24}H_{23}O_3N$	77.0 (77.2	6.2 6.2	3.8 3.8)
IIIj	$C_6H_4.CH_3$-*p*	C_4H_9-*n*	170	76	$C_{25}H_{25}O_3N$	77.6 (77.5	6.9 6.5	4.0 3.6)
IIIk	$C_6H_4.CH_3$-*p*	C_4H_9-sec.	166	55	$C_{25}H_{25}O_3N$	77.4 (77.5	6.3 6.5	3.4 3.6)
IIIl	$C_6H_4.OCH_3$-*p*	CH_3	170	50	$C_{22}H_{19}O_4N$	73.0 (73.1	5.1 5.3	3.7 3.9)
IIIm	$C_6H_4.OCH_3$-*p*	C_2H_5	185	60	$C_{23}H_{21}O_3N$	73.5 (73.6	5.3 5.6	3.6 3.7)
IIIn	$C_6H_4.OCH_3$-*p*	C_3H_7-*n*	164	70	$C_{24}H_{23}O_4N$	73.5 (74.1	5.5 5.9	3.2 3.6)
IIIo	$C_6H_4.OCH_3$-*p*	C_4H_9-*n*	175	75	$C_{25}H_{25}O_4N$	74.1 (74.4	6.1 6.2	3.1 3.4)
IIIp	$C_6H_4.OCH_3$-*p*	C_4H_9-sec.	188	60	$C_{25}H_{25}O_4N$	75.6 (74.4	6.3 6.2	3.7 3.5)

*Solvents used for crystallization were: acetic acid for IIa,b and ethanol for IIc,d and IIIa-p.

in the reactions of 3-N-(arylamido)coumarin and ethyl benzocoumarin-3-carboxylate.

Melting points are uncorrected. IR spectra in KBr were recorded on a Beckmann Accu Lab 4 instrument, PMR spectra in $CDCl_3$ on a BM 360/390 spectrometer using TMS as internal standard, and a mass spectrum on a MAT 112 instrument.

Action of arylmagnesium bromides on I

A solution of arylmagnesium bromide (0.06 mol) in dry ether (50 ml) was added in one lot to a solution of I (0.02 mol) in dry benzene (100 ml), the reaction mixture gently warmed on a water-bath for 3 hr and poured dropwise with vigorous stirring into the ice cold 10% H_2SO_4. The organic layer was separated, dried (N_2SO_4), solvent removed under reduced pressure, and the residual oil after trituration several times with pet. ether (b.p. 40-60°) gave a solid which on crystallisation furnished II (Table 1).

Action of alkylmagnesium halides on I

Compound I (0.01 mol) in dry benzene (50 ml) was treated as above with alkylmagnesium halides (0.06 mol) in dry ether (50 ml) to furnish III (Table 1).

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Polymer Supported Acetylaminophenoxide Anion: Convenient Method for O-Alkylation

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Received 19 *July* 1985; *revised and accepted* 22 *May* 1986

Alkylation of acetylaminophenoxide supported on Amberlyst A-26 gives O-alkylated products in high yields and purity. In addition to ease and simplicity of the method and regeneration of the polymeric by-product, the polymeric reagent seems to increase the nucleophilicity of the anions.

The reagents supported on insoluble polymers have found wide applications during the last decade or so in various fields, particularly in organic synthesis[1]. In continuation of our work on polymer supported reactions[2] and in view of the importance of O-alkylated acetylaminophenols as basic compounds in drug industry[3], a simple and efficient method is now reported for O-alkylation of acetylaminophenols.

Alkyl phenyl ethers are prepared by the reaction of alkyl halides with phenoxide bound to a quaternary ammonium type anion-exchange resin[4]. An improved synthesis of nitrophenyl β-D-galactopyranosides and β-D-glucopyranosides is also reported using above procedures[5]. We now report the use of anion-exchange resin for O-alkylation of acetylaminophenols. This method has the advantage of solid phase synthesis and anionic activation. Owing to the effectiveness of this system, extraordinarily mild reaction conditions can be employed.

Alkyl halides in ethanol were reacted with acetylaminophenoxide anion bound to the ion-exchange resin. Alkylation was complete within 6 to 24 hr at room temperature giving high yields of products in essentially pure form. The results are summarized in Table 1.

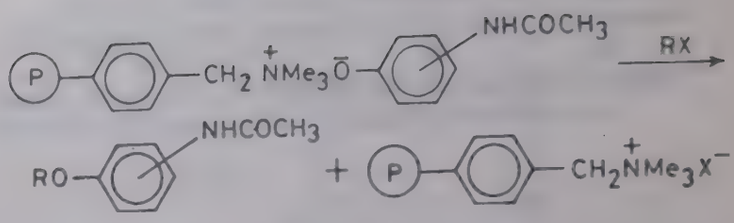

Table 1—O-Alkylation of Acetylaminophenols with Alkyl Halides at Room Temperature

Anion	Alkylating reagent	Reaction period (hr)	Yield (%)	m.p. °C
$CH_3CONH.C_6H_4.O^-$(*p*)	CH_3I	20	92	127
	C_2H_5I	16	97	135
	$CH_3(CH_2)_3Br$	20	60	125
	$C_6H_5CH_2Cl$	24	99	130
$CH_3CONH.C_6H_4.O^-$(*m*)	CH_3I	6	70	65
	C_2H_5I	6	90	92
	$C_6H_5CH_2Cl$	6	75	97
$CH_3CONH.C_6H_4.O^-$(*o*)	CH_3I	24	60	90
	C_2H_5I	24	70	80

Amberlyst A-26 acetylaminophenoxide anion

Commercial strongly basic anion exchange resin in the chloride form (Amberlyst A-26) packed in a column was washed with 5% aq. sodium salt of acetylaminophenol until complete removal of chloride ion. The resin was then successively washed with water, ethanol and benzene and finally dried *in vacuo* at 50° over phosphorus pentoxide for 12 hr. The exchange capacity was determined by passing 1 *N* aq. sodium chloride solution (100 ml) through the resin (0.3 g) in a column. The amount of acetylaminophenoxide anion in the eluate was determined by titrating with 0.01 *N* hydrochloric acid using methyl orange as indicator. The product (I) contained 1.5 m mol of acetylaminophenol per g of resin.

Alkylation procedure

Amberlyst A-26 acetylaminophenoxide anion (containing 5 mmol of acetylaminophenol) in ethanol (15 ml) was stirred with an appropriate alkyl halide (5.01 mmol) in a stoppered flask. After completion of the reaction, the resin was removed by filtration and washed with ethanol. The distillation of solvent furnished the corresponding alkylated product in a high yield in essentially pure form. The products were characterized by comparison of m.ps, IR and PMR spectra with those of authentic samples. The resin used in all cases, was easily regenerated by washing with hydrochloric acid.

One of us (DGS) is grateful to UGC, New Delhi and to Shri Swami Vivekanand Shikshan Sanstha, Kolhapur for financial assistance under the Faculty Improvement Programme.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1259-1260

Chemical Transformations of 3β-Hydroxy-3,7,7-trimethyl-bicyclo[4.1.0]heptane-4α-acetate

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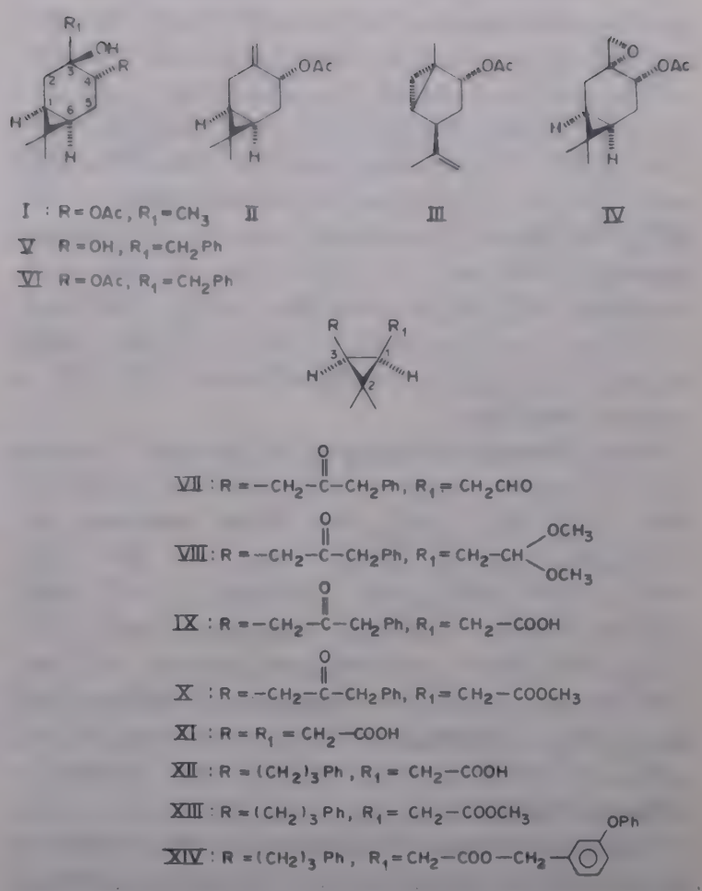
Received 2 *December* 1985; *accepted* 15 *May* 1986

The title acetate (I) has been transformed into methyl 2,2-dimethyl-3-(3-phenyl-2-oxopropyl-*cis*-cyclopropane-1-acetate (X), methyl 2,2-dimethyl-3-(3-phenyl-*n*-propyl)-*cis*-cyclopropane-1-acetate (XIII) and 3-phenoxybenzyl 2,2-dimethyl-3-(3-phenyl-*n*-propyl)-*cis*-cyclopropane-1-acetate (XIV). Some of these compounds have been tested for their insecticidal activity.

Kropp[1] has reported that the dehydration of 3β-hydroxy-3,7,7-trimethylbicyclo[4.1.0]-heptane-4α-acetate (I) by $POCl_3$/pyridine leads to a mixture of two unsaturated acetates (II) and (III). In our previous communication[2], we have reported some interesting transformations of III. herein, we report the conversion of II into methyl 2,2-dimethyl-3-(3-phenyl-2-oxopropyl)-*cis*-cyclopropane-1-acetate (X), methyl 2,2-dimethyl-3-(3-phenyl-*n*-propyl)-*cis*-cyclopropane-1-acetate (XIII) and 3 phenoxybenzyl-2,2-dimethyl-3-(3-phenyl-*n*-propyl)-*cis*-cyclopropane-1-acetate (XIV), useful intermediates[3] for the preparation of esters possessing insecticidal activity.

Epoxidation of II using *m*-chloroperbenzoic acid gave the expected[4] α-epoxide (IV), which on reaction with phenyllithium afforded in 60% yield, the solid diol (V). Purification over silica gel column followed by crystallisation from pet ether (60-80°) + 5% ethyl acetate, resulted in the pure diol (V), which analysed for $C_{16}H_{22}O_2$; m.p. 130°; M^+ 246; $[\alpha]_D^{28}$ −2.4° (*c*, 1.2, $CHCl_3$). It was fully characterised with the help of following spectral data: IR: 3400 (−OH), 1600, 1500, 700 cm^{-1} (aromatic monosubstituted); PMR (CCl_4; TMS): δ 0.7 (1H, *m*, cyclopropane proton), 0.73 and 0.95 (3H each, *s* each, *gem*-dimethyl protons), 1.23 (1H, *d*, J = 4 Hz; other cyclopropane proton), 1.83 (6H, *m*, both −OH protons and methylene protons at C-2 and C-5), 2.8 (2H, *ABq*, J = 14 Hz; $-CH_2-Ph$), 3.17 (1H, *dd*, J_1 = 7 Hz; J_2 = 9 Hz; methine proton at C-4) and 7.13 (5H, *s*, aromatic protons).

The structure of diol (V) was further confirmed by preparing its monoacetyl derivative (VI) in 80% yield as a semisolid analysing for $C_{18}H_{24}O_3$; b.p. 220° (bath)/5 mm; M^+ 288; $[\alpha]_D^{30}$ +26.4° (*c*, 0.28, $CHCl_3$); IR: 3485 (−OH), 1735, 1250 (acetate), 1600, 1500, 700 cm^{-1} (aromatic monosubstituted); PMR (CCl_4; TMS): δ 0.7 (1H, *m*, cyclopropane proton), 0.9 and 0.95 (3H each, *s*, each, *gem*-dimethyl), 1.27 (1H, *m*, other cyclopropane proton), 1.9 (3H, *s*, acetate $-CH_3$), 2.0 (5H, *m*, −OH proton and methylene protons at C-2 and C-5), 2.6 (2H, *ABq*, J = 14 Hz; CH_2-Ph), 4.43 (1H, *t*, J = 9 Hz; methine proton at C-4) and 7.0 (5H, *s*, aromatic protons).



Oxidation of the diol (V) by Jones' chromic acid reagent resulted in a complex mixture of compounds in which the desired product, i.e. the keto-acid (IX) was absent and *cis-bis*-homocaronic acid (XI) could be isolated from the reaction mixture. For this reason, the diol (V) possessing a vicinal diol group was cleaved with sodium metaperiodate to give in 80% yield, a liquid keto-aldehyde (VII) [IR: 2710 and 1715 (−CHO), 1596, 1492 and 700 cm^{-1} (aromatic monosubstituted)], which was characterized as its dimethyl acetal derivative (VIII), obtained as a liquid. It analysed for $C_{18}H_{26}O_3$; b.p. 225° (bath)/6 mm; M^+ 290; $[\alpha]_D^{28}$ −3.16° (*c*, 0.25, $CHCl_3$); IR: 1720 (keto), 1600, 1495 and 698 cm^{-1} (aromatic monosubstituted); PMR (CCl_4; TMS): δ 0.57 and 0.97 (1H each, *m* each, cyclopropane protons), 0.77 and 1.03 (3H each, *s* each, *gem*-dimethyl), 1.27 [2H, *t*, J = 6 Hz; $-CH_2-CH(OMe)_2$], 2.17 (2H, *d*, J = 6 Hz; $-CH_2-CO-$),

2.97 and 3.04 (3H each, *s* each, $2 \times CH_3O$), 3.4 (2H, *s*, $-CH_2-Ph$), 3.9 [1H, *t*, $J=6$ Hz; $-CH(OMe)_2$] and 6.73 (5H, *s*, aromatic protons).

The keto-aldehyde (VII) on oxidation by Jones' chromic acid reagent afforded in 70% yield, the keto-acid (IX) characterised as its methyl ester (X), obtained in 75% yield, as a liquid. X analysed for $C_{17}H_{22}O_3$; b.p. 236° (bath)/7 mm; M^+ 274; $[\alpha]_D^{28}$ −6.2° (*c*, 1.83, $CHCl_3$); IR: 1735 (keto and ester $\geq C=O$), 1605, 1505 and 710 cm^{-1} (aromatic monosubstituted); PMR (CCl_4): δ 0.86 and 1.16 (1H each, *m* each, cyclopropane protons), 0.94 and 1.21 (3H each, *s* each, *gem*-dimethyl), 2.03 (2H, *d*, $J=6$ Hz; $-CH_2-COOMe$), 2.26 (2H, *d*, $J=6$ Hz; $-CH_2-CO-$), 3.51 (3H, *s*, ester $-CH_3$), 3.55 (2H, *s*, $-CH_2-Ph$) and 7.02 (5H, *s*, aromatic protons).

Huang-Minlon reduction of X furnished the acid (XII; 70% yield) which was converted into its methyl ester (XIII; 85% yield) as a liquid analysing for $C_{17}H_{24}O_2$; b.p. 195° (bath)/5 mm; M^+ 260, $[\alpha]_D^{28}$ +8.6° (*c*, 0.85, $CHCl_3$); IR: 1730 (ester $\geq C=O$), 1600, 1498 and 700 cm^{-1} (aromatic monosubstituted); PMR (CCl_4): δ 0.6 (2H, *m*, cyclopropane protons), 0.87 and 1.06 (3H each, *s* each, *gem*-dimethyl), 2.13 (2H, *d*, $J=8$ Hz; $-CH_2-COOMe$), 2.57 (2H, *t*, $J=9$ Hz, $-CH_2-Ph$), 3.57 (3H, *s*, ester $-CH_3$) and 7.0 (5H, *s*, aromatic protons).

Transesterification of XIII with *m*-phenoxybenzyl alcohol afforded, the ester (XIV, 73% yield) which was purified by column chromatography over silica gel. The ester (XIV), a liquid, analysed for $C_{29}H_{32}O_3$; M^+ 428; $[\alpha]_D^{26}$ +2.9 (*c*, 1.7, $CHCl_3$); IR: 1720 (ester $\geq C=O$), 1595, 1486 and 695 cm^{-1} (aromatic); PMR (CCl_4): δ 0.63 (2H, *m*, C-1 and C-3 cyclopropane protons), 0.96 and 1.03 (3H each, *s* each, *gem*-dimethyl), 1.63 to 1.93 (4H, *m*, methylene protons at C-3 side chain), 2.23 (2H, *d*, $J=6$ Hz; $-CH_2-COO-$), 2.6 (2H, *t*, $J=6$ Hz; benzylic $-CH_2-$ at C-3 side chain, 5.6 (2H, *s*, ester benzylic $-CH_2-$), 7.15 (14H, *m*, aromatic protons).

Compound (X) exhibited insecticidal activity against *Aedes aegypti* and *Anopheles stephensi* showing 100% and 80% mortality respectively at 250 ppm dose.

The compounds (XIII) and (XIV) exhibited insecticidal activity against *Culex fatigens* and *Anopheles stephensi*. Compound (XIII) showed 100% and 60% mortality at 250 ppm dose against *Culex fatigens* and *Anopheles stephensi* respectively while XIV showed 60% mortality only against *Culex fatigens* at the same dose.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1261-1262

Synthesis & Alkylation of Bis(9-anthryl) Disulphide

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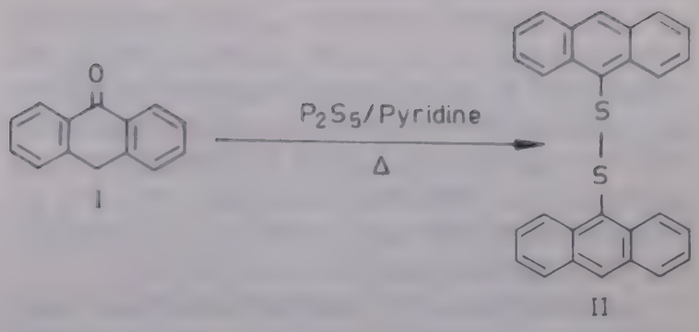
Received 3 *October* 1985; *revised and accepted* 20 *May* 1986

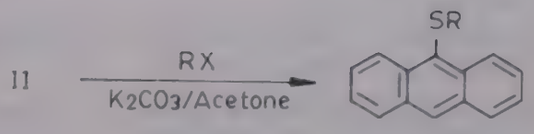
Reaction of anthrone with P_2S_5 affords the title compound in 90% yield instead of the expected thioanthrone. The resultant disulphide when alkylated with methyl iodide, ethyl iodide, allyl bromide and propargyl bromide gives the corresponding S-alkylated anthracenes.

During our study on the synthesis of heterocyclic compounds we became interested in the preparation of 9-S-allyl- and 9-S-propynylanthracenes as potential intermediates. The usual route involves the reaction of alkyl halides with anthracene-9-thiol. But the preparation of the latter compound is much complicated as it involves the reaction of anthracene with S_2Cl_2 and other reagents in three steps[1]. Another route for preparing these compounds by the S-alkylation of thioanthrone was also considered as O-alkylation of acridone[2-6], anthrone[7] and S-alkylation of thioacridone[8,9] have already been studied.

In our attempt to prepare thioanthrone, a hitherto unreported compound, by treating anthrone (I) with P_2S_5 in pyridine, a yellow crystalline solid (II; m.p. 204°) was obtained in 90% yield. Unexpectedly this product did not show signals for benzylic hydrogens in the PMR spectrum and for benzylic carbon in the ^{13}C NMR spectrum. Its mass spectrum exhibited the molecular ion peak at *m/z* 418 corresponding to the dimeric form. So the product was characterized as bis(9-anthryl) disulphide (II). This compound (m.p. 233°) was prepared in 1922 from anthracene-9-thiol which in turn was obtained by a complicated procedure[1], the yield was not even mentioned and the procedure was not found to be easily reproducible. In this respect the reaction of anthrone with P_2S_5 offers a simple method for the preparation of II in a very high yield.

The disulphide II on treatment with methyl iodide, ethyl iodide, allyl bromide and propynyl bromide in acetone containing anhyd. K_2CO_3 gave the corresponding 9-S-alkylated anthracenes (III). 9-Methylmercaptonanthracene (IIIc) was characterised by comparison (m.m.p.) with an authentic sample prepared by the literature procedure[10].





IIIa, R = $CH_2-C\equiv CH$
b, R = $CH_2-CH=CH_2$
c, R = CH_3
d, R = CH_2CH_3

Bis(9-anthryl disulphide (II)

A mixture of I (5.3 g; 0.03 mol), P_2S_5 (6.6 g; 0.03 mol) and anhyd. pyridine (80 ml) was refluxed for 5 hr, cooled and poured into water. The reddish crystalline product was filtered, washed with dil. HCl followed by water, and crystallised from ethanol to give II as a yellow crystalline solid, m.p. 204°, yield 90% (5.6 g) (Found: C, 80.1; H, 4.0. $C_{28}H_{18}S_2$ requires C, 80.0, H, 4.3%); IR (KBr): 1610, 1500 and 1430 cm^{-1}; PMR ($CDCl_3$; 90 MHz): δ 7.0-8.4 (*m*, 18 H); MS: *m/z* 418; UV (EtOH): 252, 368, 385 nm.

Reaction of II with propargyl bromide

Propargyl bromide (1.2 g; 0.01 mol) was added to a mixture of II (2.1 g; 0.01 mol), K_2CO_3 (2 g) and dry acetone (100 ml) while stirring in N_2 atmosphere under reflux and the reaction continued for 8 hr. After removal of acetone, the mixture was extracted with chloroform, washed thoroughly with water and dried (Na_2SO_4). Removal of solvent gave a solid mass which was purified by passing through a silica gel column and eluting with pet. ether (60-80°) to give 9-propynylmercaptoanthracene (IIIa), m.p. 212°, yield 30% (0.75 g) (Found: C, 81.9; H, 4.6. $C_{17}H_{12}S$ requires C, 82.3; H, 4.8%); IR (KBr): 3270(s) and 2020 cm^{-1} (w) for $-C\equiv C-H$ stretching; PMR ($CDCl_3$; 90 MHz): δ 2.0-2.1 (*t*, 1H, $-C\equiv CH$), 3.55-3.60 (*d*, 2H, $S-CH_2$), 7.0-9.1 (*m*, 9H, Ar-*H*); MS: *m/z* 248 (M^+).

Reaction of II with allyl bromide under similar conditions furnished IIIb as a viscous oil, yield 30% (0.75 g) (Found: C, 81.0; H, 5.2. $C_{17}H_{14}S$ requires C, 81.6; H, 5.6%); PMR ($CDCl_3$; 90 MHz): δ 3.4-3.5 (*d*,

2H, S-CH_2), 4.6-4.8 (*m*, 2H, $-CH=CH_2$), 5.6-6.1 (*m*, 1H, $-CH=CH_2$), 7.4-9.1 (*m*, 9H, Ar-*H*).

Reaction of II with methyl iodide

Methyl iodide (0.01 mol) was added to a mixture of I (0.01 mol), K_2CO_3 (2 g) and acetone (100 ml) and refluxed for 8 hr. After removal of acetone, the mixture was extracted with chloroform, washed thoroughly with water and dried (Na_2SO_4). Solvent was removed and the residue when chromatographed over silica gel column furnished IIIc as a solid (m.p. 157°, yield 30%) and the unreacted starting material II (30%).

A similar reaction of II with ethyl iodide gave IIId as a solid (m.p. 97 , yield 35%) and the unreacted starting material II (35%).

We thank Prof. J W Lown of the University of Alberta, Canada for mass spectrum of II, the University of Kalyani and the CSIR, New Delhi, for financial assistance.

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Indian Journal of Chemistry
Vol. 25B, December 1986, p. 1263

A New Synthetic Route to Aromatic Glyoxals

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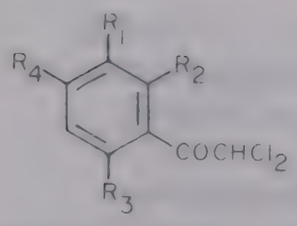
Received 5 *February* 1986; *accepted* 14 *April* 1986

Dichloroacylation of toluene, *o*- and *m*- xylenes, chloro- and bromo-benzenes and *m*-chlorotoluene under Friedel-Crafts conditions leads to the corresponding chloroketones (Ia-f) which on controlled hydrolysis afford the glyoxals (IIa-f) respectively.

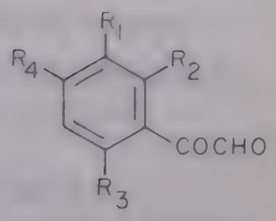
A number of methods are available[1-4] for the synthesis of aromatic glyoxals, a class of compounds of importance in medicinal chemistry. However, most of these methods involve costly reagents or are less attractive due to lengthy synthetic strategy and formation of byproducts. The present note deals with a new synthetic route to aromatic glyoxals, which consists of dichloroacetylation of the substrates under Friedel-Crafts conditions and subsequent controlled hydrolysis of the resultant products. The new synthesis corroborates the mechanism that mandelic acids result from dihaloketones most plausibly through intramolecular cross Cannizzaro reaction of the intermediate α-ketoaldehydes under the influence of caustic soda solution[5].

In carrying out dichloroacetylation of the substrates under Friedel-Crafts conditions no solvent was used. The temperature of the reaction was maintained at 0-5°. In the case of *m*-chlorotoluene the reaction was carried out at 10-15°. An example of the synthesis is provided with toluene as the substrate.

Toluene was reacted with dichloroacetyl chloride in the presence of anhydrous $AlCl_3$ at 0-5°. The product after being decomposed with ice-HCl mixture was steam distilled to remove unreacted toluene. The resulting chloroketone (I) was taken up in ether, washed free from acid and purified by distillation, b.p. 110°/10 mm, yield 95%. The chloroketone when subjected to hydrolysis with 15% aq Na_2CO_3 under gently refluxing condition led to 4-methylphenylglyoxal (II) which was isolated by distillation with steam, m.p. (hydrate) 105°, yield 90%.



(I)



(II)

Table 1 — Substrates, Their Chloroketones (I) and Glyoxals (II)

Substrate	Chloroketone (I) b.p./10 mm (yield)	Glyoxal (II) b.p. (yield)
Toluene	a: $R_1=R_2=R_3=H$; $R_4=CH_3$ 110° (95%)	a: $R_1=R_2=R_3=H$; $R_4=CH_3$ Hydrate, m.p. 104-6° (90%)
o-Xylene	b: $R_2=R_3=H$; $R_1=R_4=CH_3$ 145-46° (92%)	b: $R_2=R_3=H$; $R_1=R_4=CH_3$ 125-30°/30 mm (65%)
m-Xylene	c: $R_1=R_3=H$; $R_2=R_4=CH_3$ 139-44° (90%)	c: $R_1=R_3=H$; $R_2=R_4=CH_3$ 115-20°/10 mm (80%)
Chlorobenzene	d: $R_1=R_2=R_3=H$; $R_4=Cl$ 128° (70%)	d: $R_1=R_2=R_3=H$; $R_4=Cl$ hydrate, m.p. 120° (78%)
Bromobenzene	e: $R_1=R_2=R_3=H$; $R_4=Br$ 150° (60%)	e: $R_1=R_2=R_3=H$; $R_4=Br$ 115-20°/10 mm (75%)
Chlorotoluene	f: $R_1=R_3=H$; $R_2=CH_3$, $R_4=Cl$ 141-45° (70%)	f: $R_1=R_3=H$; $R_2=CH_3$, $R_4=Cl$ 90-95°/10mm (60%)

All the chloroketones and glyoxals obtained from various substrates (Table 1) were characterised by their analytical and spectral (IR and PMR) data and also by comparison of their physical data with those reported in literature.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1264-1265

Partial Deallylation of 3,3-Diallyl-1,2,3,4-tetrahydroquinolin-2,4-diones by Sodium Hydrogen Telluride

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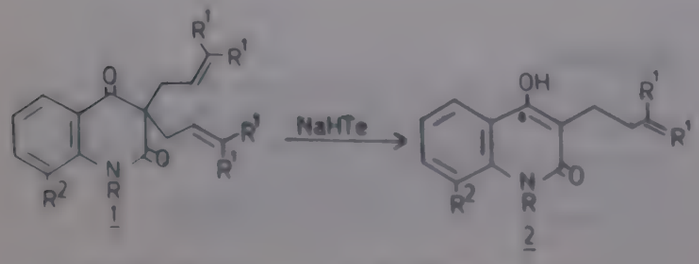
Received 17 *March* 1986; *accepted* 12 *May* 1986

3,3-Diallyl-1,2,3,4-tetrahydroquinolin-2,4-diones (**1**) readily undergo partial deallylation to give the corresponding 3-allyl-4-hydroxyquinolin-2(1*H*)-ones (**2**) on treatment with sodium hydrogen telluride in boiling ethanol.

Sodium hydrogen telluride has earlier been shown by Shanmugam and coworkers[1] to serve as a convenient reducing agent for t eh hydrogenation of 3-vinylquinolines as well as α,β-unsaturated carbonyl compounds. Since then several reports[2-6] have appeared in literature describing its use as a reductant for various types of functional groups. Presently we have found that this reagent can be effectively used for the partial deallylation of 3,3-diallyl-1,2,3,4-tetrahydroquinolin-2,4-diones (**1**) to give the corresponding 3-allyl-4-hydroxyquinolin-2-(1*H*)-ones (**2**).

The 3,3-diallylquinoline system (**1**) has been found[7,8] to occur in compounds occurring in several species of the Rutaceae, as well as encountered[9-13] in the base-catalysed allylation of 4-hydroxyquinolin-2-(1*H*)-ones. The conversion of buchapsine [3-1,1-dimethylallyl)-3-(3,3-dimethylallyl)1,2-dihydroquinolin-2,4-dione] by heating with acetic anhydride and sodium acetate to **2b** (as its acetate) as one of the products, appears to be the only instance hitherto recorded[13] of such a deallylation reaction. But **1b** remained intact and did not give rise to **2b** even after prolonged boiling with acetic anhydride and sodium acetate. It was contented[13] that the steric crowding at the C_3-quarternary carbon atom of buchapsine might have induced the cleavage of the 1,1-dimethylallyl group. Hence the titled reagent appears to be unique and general one for the neat transformation of **1** to **2**. Since prenylquinolones such as **2b** have been recognised as precursors[14,15] both in organic synthesis[14,15] and biosynthesis[14] to the prenyl-, furo-, and pyrano-quinoline alkaloids, the realisation of such a process is considered worthwhile.



a: R = R¹ = R² = H; b: R = R² = H; R¹ = CH₃;
c: R = R¹ = CH₃, R² = H; d: R = R¹ = H, R² = OCH₃;
e: R = H, R¹ = CH₃; R² = OCH₃.

General Procedure

To a solution of sodium hydrogen telluride prepared *in situ* from tellurium powder (1.3 g) and sodium borohydride (0.9 g) in ethanol (20 ml), buffered to *p*H 7.5 by adding deoxygenated acetic acid, was added **1** (0.005 mol) and the mixture refluxed under nitrogen blanket for 4-6 hr, filtered, the filtrate evaporated, the residue dissolved in water and acidified to give **2**.

The products formed (Table 1) were identified by direct comparison (co-TLC, co-IR, m.m.p.) with authentic samples.

Table 1—Partial Deallylation Using Sodium Hydrogen Telluride

Substrate	Time of reflux hr	Product	Yield %
1a[9]	4	**2a**[9]	80
1b[10]	5.5	**2b**[15]	75
1c[11]	4	**2c**[16]	75
1d[a]	5	**2d**[a]	80
1e[12]	5	**2e**[15]	70

a **1d**, m.p. 78-80 ; **2d**, m.p. 198-200°, spectral and analytical data were in conformity with the structures assigned.

We thank the CSIR, New Delhi for the award of a senior research fellowship to one of us (NS) and Mr M Palaniswamy for the spectral data.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1266-1268

Condensed Heterocycles: Synthesis of 2-Aryl-5-oxo-5-*H*-pyrido-[3′,2′:5,6]pyrimido[2,1-*b*][1,3,4]-oxadiazoles/thiadiazoles, 9-Aryl-5-oxo-5*H*-pyrido[3′,2′:5,6]pyrimido[2,1-*b*]-thiadiazoles & 2-Aryl-6-hydroxy[1,3,4]-thiadiazolo/thiazolo[3,2-*a*]-benzimidazoles

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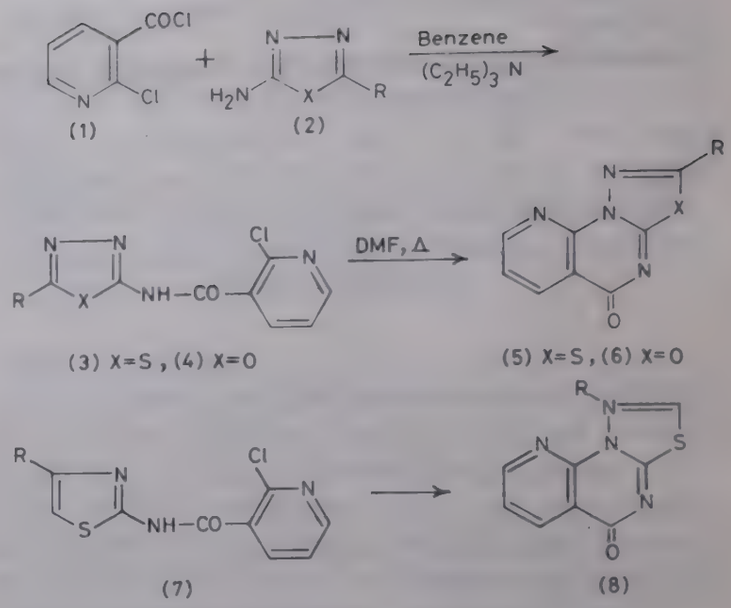
Received 13 *August* 1985; *revised and accepted* 28 *April* 1986

A few bridgehead nitrogen containing heterocycles such as 2-aryl-5-oxo-5*H*-pyrido[3′,2′:5,6]pyrimido[2,1-*b*]thiadiazoles/oxadiazoles (**5** and **6**) and 9-aryl-5-oxo-5*H*-pyrido[3′2′:5,6]pyrimido[2,1-*b*]thiazoles (**8**) have been prepared by the reaction of 2-chloropyridine-3-carbonyl chloride with various 2-amino-oxa/thiadiazoles and thiazoles respectively. Condensed heterocycles such as 2-aryl-6-hydroxy-1,3,4-thiadiazolo[3,2-*a*]benzimidazoles (**10**) and 2-aryl-6-hydroxythiazolo[3,2-*a*]benzimidazoles (**13**) have also been prepared from the condensation of aminoheterocycles with *p*-benzoquinone. The structures of these compounds have been established by elemental analyses and spectral data.

The importance of thia/oxadiazole[1] and thiazole[2] compounds is well established in the fields of pharmaceutical chemistry and plant and animal biochemistry. The syntheses of condensed heterocycles possessing these units such as 2-aryl-6-carboethoxy-5*H*-1,3,4-thia/oxadiazolo[3,2-*a*]pyrimidin-5-ones and their isomeric C-5 and C-7 carboethoxy analogues from the reactions of aminoheterocycles with different types of electrophilic reagents have been reported by us in our previous communications[3] as potential antimicrobial and antitumor agents. In the present study we have synthesised the title heterocyclic systems by the reaction of heterocyclic amines with 2-chloropyridine-3-carbonyl chloride (**1**) and *p*-benzoquinone. The reaction of aminoheterocycles with **1** in benzene or toluene in the presence of Et_3N gave urea intermediates (**3** or **4**) which underwent cyclisation in DMF to furnish 2-aryl-5-oxo-5*H*-pyrido[3′,2′:5,6]pyrimido[2,1-*b*][1,3,4]thiadiazoles or oxadiazoles (**5** or **6**; Table 1). Thus, 2-amino-1,3,4-thiadiazole reacted with **1** to furnish the urea derivative **3a** (R = H; X = S) which showed νNH and νC=O at 3250 and 1680 cm^{-1} respectively. Cyclisation of **3a** gave the corresponding cyclic compound **5a** which showed νC=O at 1630 cm^{-1} (the band for the −NH− group was absent). The PMR spectrum of **3a** in DMSO-d_6 exhibited a four-proton multiplet centered at δ 8.25 assignable to the pyridine ring protons and C_5−H of thiadiazole ring. The D_2O exchangeable NH proton appeared as a broad band centered at δ 5.6. The PMR spectrum of the cyclised product (**5a**) did not show any exchangeable proton and exhibited only a downfield multiplet (δ 8.45) due to pyridine and C_5−H thiazole protons. Similar IR spectral characteristics were observed in case of the other products given in Table 1. Similarly, 4-substituted 2-aminothiazoles reacted with **1** to give **7** which underwent cyclisation affording 9-aryl-5-oxo-5*H*-pyrido[3′2′:5,6]pyrimido[2,1-*b*]thiazoles (**8**; Table 1). Their structures were also established by spectral data.



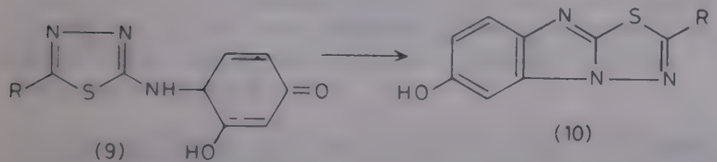
(2-8) a, R=H; b, R=Ph; c, R=p-Anisyl; d, R=p-Cl-Ph

2-Aryl-6-1,3,4-hydroxythiazolo[3,2-*a*]benzimidazoles (**10**) were prepared by the acid catalysed cyclodehydration of aminoheterocycles with *p*-benzoquinone in acetic acid. The reaction involves an initial nucleophilic attack of the amino group at the carbonyl carbon to give the unstable intermediate **9**, which undergoes cyclodehydration to give **10** by attack at the *ortho*-carbon through imino nitrogen. The UV spectrum of **10a** (R = H), prepared from 2-amino 1,3,4-thiadiazole with *p*-benzoquinone in neutral ethanol, showed three bands at 245 (log ε 4.6), 270 (4.0) and 360 nm (4.2). The absorption bands underwent a bathochromic shift in 0.1 *M* HCl [λ_{max} at 320 (log ε 4.3) and 380 nm (4.4)] and 0.1 *M* NaOH [λ_{max} at 320 (log ε 4.1) and 450 nm (4.5)] solutions. The greater shift in alkaline medium may be due to quinonoid structure as

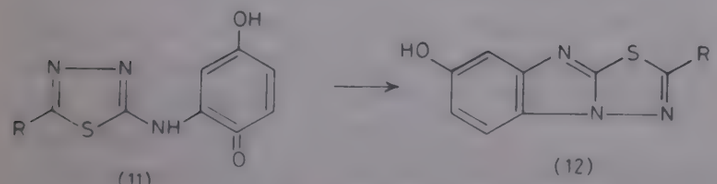
Table 1 – Characterisation Data of Chloropyridine Carboxamides (**3**, **4** and **7**) and Pyridopyrimidones (**5**, **6** and **8**)

Compd	m.p. °C	Mol. formula	Sulphur (%)	
			Found	Calc.
3b	196	$C_{14}H_9N_4SOCl$	10.1	10.1
3c	187	$C_{15}H_{11}N_4SO_2Cl$	9.1	9.2
3d	172	$C_{14}H_8N_4SOCl$	9.2	9.5
4b	175	$C_{14}H_9N_4O_2Cl$	11.7	11.8*
4c	188-89	$C_{15}H_{11}N_4O_3Cl$	10.8	10.7*
5b	252-55	$C_{14}H_8N_4SO$	11.5	11.4
5c	>260	$C_{15}H_{10}N_4SO_2$	10.2	10.3
5d	>260	$C_{14}H_7N_4SOCl$	10.2	10.2
6b	>260	$C_{14}H_8N_4O_3$	—	—
6c	>260	$C_{15}H_{10}N_4O_3$	—	—
7b	188	$C_{15}H_{10}N_3SOCl$	10.1	10.2
7c	178	$C_{16}H_{12}N_3SO_2Cl$	9.1	9.1
7d	162	$C_{15}H_9N_3SOCl_2$	9.3	9.1
8b	>260	$C_{15}H_9N_3SO$	11.4	11.5
8c	>260	$C_{16}H_{11}N_3SO_2$	10.2	10.4
8d	>260	$C_{15}H_8N_3SOCl$	9.1	9.0

* Indicates percentage of chlorine.



(9) (10)



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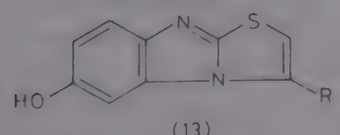

(13)

(9-13) a, R=H; b, R=Ph

one of the contributing forms. However, the slight shift in acid solution is ascribable to the salt formation. The possibility for the formation of 7-hydroxy-1,3,4 thiadiazolo [3,2-*a*]benzimidazole (**12**) through the initial attack of nitrogen nucleophile at the electrophilic *meta*-carbon with respect to carbonyl group and subsequent cyclodehydration was ruled out because **12** cannot give rise to quinonoid structure and the spectral behaviour of the compound cannot be explained. This type of change in structures at different *p*H values has been observed by other workers[4] also.

All melting points are uncorrected. IR and UV spectra of the compounds were recorded on a Perkin-Elmer Model-293 and a Beckman Model-35 spectrophotometers respectively.

N-(1,3,4-*Thiadiazol*-2-*yl*-2-*chloropyridine*-3-*carboxamide* (**3a**)

A mixture of 2-chloronicotinic acid (1.5 g) and thionyl chloride (5 ml) was refluxed under stirring for 3 hr, excess of thionyl chloride distilled off and benzene (5 ml) added to remove the last trace of thionyl chloride. The resulting crude 2-chloronicotinoyl chloride (**1**) was dissolved in toluene (25 ml) and added dropwise with stirring to a solution of 2-amino-1,3,4-thiadiazole (1 g) in toluene (25 ml) and triethylamine (1 ml). After the addition, the mixture was heated under reflux further for 3 hr and cooled. The solid obtained was filtered, dried in air and recrystallised from ethanol to give **3a**, m.p. 110°, yield 1.2 g (54%) (Found: S, 13.2. $C_8H_5N_4SOCl$ requires S, 13.3%).

5-*Oxo*-5*H*-*pyrido*[3',2':5,6]*pyrimido*[2,1-*b*][1,3,4]*thiadiazole* (**5a**)

A solution of **3a** (0.7 g) in dimethylformamide (10 ml) was heated slowly under reflux for 2 days. On cooling it furnished the desired product (**5a**) as fine needles, m.p. 153°, yield 400 mg (60%) (Found: S, 15.5. $C_8H_4N_4SO$ requires S, 15.7%); IR: 1630 cm^{-1} (C=O).

6-*Hydroxy*-1,3,4-*thiadiazolo*[3,2-*a*]*benzimidazole* (**10a**)

A solution of *p*-benzoquinone (1.1 g) in gl. acetic acid (10 ml) was added dropwise to a solution of 2-amino-1,3,4-thiadiazole (1 g) with stirring. The mixture was heated at 70-80° for 8 hr and kept overnight. The solvent was removed by passing a current of air through the reaction mixture on a water-bath. The residue was triturated with water (10 ml), filtered, washed with water to make it free from acetic acid and extracted with 10% H_3PO_4. The brown coloured extract was neutralised with aq. sodium carbonate to give the desired product **10a**, m.p. 237° (d), yield 10.6 g (46%) (Found: S, 16.6. $C_8H_5N_3SO$ requires S, 16.8%).

The other benzimidazole derivatives prepared by a similar procedure are as follows:

10b: m.p. >280 (Found: S, 11.6. $C_{14}H_9N_3SO$ requires S, 12.0%); UV (EtOH): 225, 265, 350 nm; UV (0.1 *M* HCl): 325, 385 nm; UV (0.1 *M* NaOH): 340, 460 nm).

13a: m.p. >280 (Found: S, 16.52. $C_9H_6N_2SO$ requires S, 16.8%); UV (EtOH): 250, 260, 350 nm; UV (0.1 *M* HCl): 305, 390 nm; UV (0.1 *M* NaOH): 340, 460 nm.

13b: m.p. >28 (Found: S, 12.1. $C_{15}H_{10}N_2SO$ requires S, 12.0%).

The authors are grateful to CSIR, New Delhi for the award of a research fellowship to one of them (MS).

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1269-1272

Condensed Tetrahydrobenzothiazoles: Part IV – Synthesis of Some 2-Substituted 4,5,6,7-Tetrahydrobenzothiazoles & Their 5,5-Dimethyl-7-oxo Derivatives

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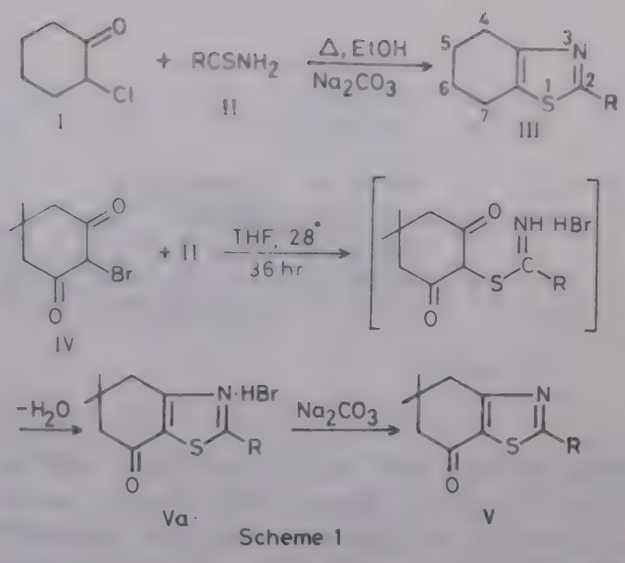
Received 4 *November* 1985; *revised and accepted* 3 *March* 1986

Condensation of 2-chlorocyclohexanone (I) with substituted thioamides (II) in hot ethanol affords 2-substituted 4,5,6,7-tetrahydrobenzothiazoles (III). A similar reaction of 2-bromodimedone (IV) with II does not give 2-substituted 5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzothiazoles alone (V); a gummy product containing more than two compounds (TLC) is obtained in each case. However, when the reaction is carried out in THF at room temperature for 36 hr, the expected hydrobromide salts (Va) are obtained in excellent yields. The free bases (V) are liberated from Va by treatment with Na_2CO_3 solution. Structures of III, Va and V have been established by elemental analyses and spectral data. They do not exhibit any significant antifungal or antibacterial activity *in vitro*.

In continuation of our work[1-3] on condensed tetrahydrobenzothiazoles of pharmacological significance, we wish to report in this note the synthesis and antimicrobial properties of some 2-arylamino-4,5,6,7- and 2-substituted 5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzothiazoles (III and V).

The condensation of 2-chlorocyclohexanone (I) with 1-arylthioureas (II, R = NHAr) in boiling ethanol for 12 hr followed by treatment of the product with sodium carbonate solution afforded III in good yields (Scheme 1; Table 1). A similar reaction of 2-bromodimedone (IV) with II did not give pure V and gummy product was obtained which on TLC (benzene: ethyl acetate-92:8; v/v) showed the presence of more than two compounds preceded by tailing in each case. No solid product could be obtained by crystallisation or chromatography of the gummy mass. So we followed a direct method reported by Pujari *et al.*[4] using NBS, dimedone and II in one-pot reaction, and the yields of V were poor (~30%). Then King's modification[5-7] using dimedone, powdered iodine and II in 1:1:2 molar ratio was tried, but a tarry product was obtained in most cases. We have already reported[1] the short-comings of this modification.

Taking into consideration the lability of bromine atom and the reactivity of α-methylene group of IV, it



Scheme 1

was contemplated to carry out the condensation of II and IV at room temperature for a longer period using a polar solvent such as THF. As a result, a hydrobromide salt separated out within 3 hr, but the mixture was stirred for 36 hr to ensure completion of the reaction. The hydrobromides (Va) on treatment with aq. sodium carbonate solution gave the corresponding free bases (V) (Scheme 1; Table 2). The structures III, Va and V were established by elemental analyses and spectral data. Compounds Va were characterised for carbonyl group by preparation of their 2,4-DNP derivatives. The structure V was further confirmed by reduction of V_{22} with PI_3 to the known 2-amino-5,5-dimethyl-4,5,6,7-tetrahydrobenzothiazole[8], m.p. 208° (m.m.p. of this compound with V_{22}, 182°).

Okamiya[9] proposed a mechanism for Hantzsch's thiazole synthesis and showed it to be a bimolecular reaction involving formation of isothiouronium salt which undergoes dehydrocyclisation on heating or standing for a longer period to form the thiazole ring. This has been further substantiated by Shadbolt[10] who identified the intermediate isothiouronium salt in keto-form by IR and PMR spectra during the reaction of phenacyl bromide with mercaptoimidazole in acetone at room temperature. In the present case, heating might have resulted in hydrogen bonding and/or degradation due to the oxo group in ethanolic medium giving rise to a gummy product. Hence, we preferred to carry out the reaction at room temperature for a longer period using THF as a solvent.

Biological activity

All the compounds were screened *in vitro* at 100 ppm concentrations for their antifungal activity against

† Taken from the Ph.D. Thesis of V T U.

Table 1 – Characterisation Data of 2-arylamino-4,5,6,7-tetrahydrobenzothiazoles (III)

Compd	R	Yield (%)	m.p. C	Mol. formula	N(%) Found	N(%) Calc.
1	α-$C_{10}H_7NH$–	60	186	$C_{17}H_{16}N_2S$	10.2	10.0
2	β-$C_{10}H_7NH$–	75	138-39	$C_{17}H_{16}N_2S$	9.8	10.0
3	p-$NO_2C_6H_4NH$–	53	144-45	$C_{13}H_{13}N_3O_2S$	15.1	15.3
4	$C_6H_5CH_2NH$–	58	120-21*	$C_{14}H_{16}N_2S$	11.3	11.5
5	4-Cl-2-CH_3–C_6H_3NH–	70	128	$C_{14}H_{15}ClN_2S$	10.0	10.1
6	2-Cl-4-CH_3–C_6H_3NH–	72	104-105	$C_{14}H_{15}ClN_2S$	10.2	10.1
7	4-Br-2-CH_3–C_6H_3NH–	63	140-42	$C_{14}H_{15}BrN_2S$	8.6	8.7
8	2-Br-4-CH_3–C_6H_3NH–	68	111-12	$C_{14}H_{15}BrN_2S$	8.8	8.7
9	5-Cl-2,4-$(OCH_3)_2$–C_6H_2NH–	75	138-40	$C_{15}H_{17}ClN_2O_2S$	8.5	8.6

*lit.[7] m.p. 118°.

Candida albicans and *Aspergillus niger*, and for antibacterial activity against *Staphylococcus aureus* and *Eschirichia coli* by the cup-plate method[11]. Compounds Va in general displayed better activity than III and V. These compounds were not promising except III_5, III_7, Va_{15}, Va_{17}, V_{15}, V_{18} and V_{24} as antifungal agents.

Melting points were determined in glass capillaries and are uncorrected. IR spectra were run on a Perkin-Elmer 337 Infracord spectrophotometer (ν_{max} in cm^{-1}), and PMR spectra in $CDCl_3$ on a Varian A-60 spectrometer using TMS as an internal standard (chemical shifts in δ, ppm). Thiourea, thioacetamide, thiobenzamide, thiosemicarbazide, cyclohexanone and dimedone were commercial samples and were used in the reaction after purification. The known thioureas used in this study were prepared by literature method[12-16].

New 2-methyl-4-chlorophenylthiourea (m.p. 174-75°), 2-methyl-4-bromophenylthiourea (m.p. 262°), 2-chloro-4-methyl-phenylthiourea (m.p. 158°) and 2-bromo-4-methylphenylthiourea (m.p. 171°) were prepared by the usual method[13]. They analysed correctly for nitrogen. 2-Chlorocyclohexanone[17] and 2-bromodimedone[18] were prepared in good yields.

2-*Arylamino*-4,5,6,7-*tetrahydrobenzothiazoles* (*III*): *General procedure*

A mixture of arylthiourea (0.03 mol) and freshly distilled I (4 g, 0.03 mol) in ethanol (50 ml) was heated to boiling on a steam-bath for 12 hr, solvent removed under reduced pressure, and the residue washed with a small volume of ether, basified with cold aq. ammonia and left overnight. The solid that separated was filtered and crystallised from ethanol as needles, plates. Their characterisation data are given in Table 1; IR: 3190 ± 25 (NH), 1545 ± 10 (thizole C=N) and 860-690 (aromatic CH bending); PMR: ~1.75 (*m*, 4H, 5-CH_2 + 6-CH_2), 2.55 (*m*, 4H, 4-CH_2 + 7-CH_2) and 8.20-6.90 (aryl and exchangeable NH protons).

2-*Substituted* 5,5-*dimethyl*-7-*oxo*-4,5,6,7-*tetrahydrobenzothiazoles* (*V*): *General procedure*

A mixture of 2-bromodimedone (3.3 g, 0.015 mol) and II (0.015 mol) in THF (50 ml) was stirred at room temperature for 36 hr. The resultant hydrobromide (Va) was filtered, washed with a small quantity of THF and dried in air. The combined filtrate on concentration to about 10 ml *in vacuo* gave an additional amount of Va. Compounds Va, thus prepared, gave positive test for the presence of a keto group with 2,4-DNP. The characterisation data of Va and the free bases (V), obtained by basification of Va with saturated aq. sodium carbonate solution, are given in Table 2. In case of reaction with thiosemicarbazide, the hydrobromide salt did not separate out. The reaction mixture was directly basified to give the base V_{23} (Table 2). The free bases were crystallised from benzene-pet. ether. The IR spectra of V_{1-17} exhibited bands at 3350 ± 30 (NH), 1680 ± 10 (C=O), 1550 ± 10 (C=N), 1385-1380 doublet (*gem*-dimethyl and 860-690 (aromatic CH bending). The PMR spectra of V_1, V_5 and V_{12} displayed signals around 1.13 (*s*, 6H, *gem*-dimethyl), 2.51 (*s*, 2H, 4-CH_2), 2.11 (broad *s*, 2H, 6-CH_2) and 8.28-6.85 (NH and Ar–H). Compounds V_8 and V_{15} showed an additional singlet at 2.21 due to CH_3 protons of benzene ring. Pujari *et al.*[19] have reported chemical shifts at 2.60 (*s*, 5-CH_2) and 2.90 (*s*, 7-CH_2) for 2-(*p*-chlorophenyl)-6,6-dimethyl-8-oxo-imidazo[2,1-*b*]5,6,7,8-tetrahydrobenzothiazole which are not in agreement with our assignments.

We are grateful to UGC, New Delhi for the award of a teacher fellowship to one of us (V T U).

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Table 2 – 2-Substituted 5,5-Dimethyl-7-oxo-4,5,6,7-tetrahydrobenzothiazoles (V) and Their Hydrobromides (Va)

Compd	R	Hydrobromide (Va)					Tetrahydrobenzothiazole (V)				
		Yield (%)	m.p. °C	Mol formula	N(%)		Yield (%)	m.p. °C	Mol. formula	N(%)	
					Found	Calc.				Found	Calc.
1	C_6H_5NH-	80	224(d)	$C_{15}H_{17}BrN_2OS$	8.2	7.9	68	164-65	$C_{15}H_{16}N_2OS$	10.5	10.3
2	$C_6H_5CH_2NH-$	73	204(d)	$C_{16}H_{19}BrN_2OS$	7.9	7.6	74	158(d)	$C_{16}H_{18}N_2OS$	10.0	9.8
3	o-Cl – C_6H_4NH-	76	>250	$C_{15}H_{16}BrClN_2OS$	7.5	7.2	70	172-73	$C_{15}H_{15}ClN_2OS$	9.0	9.1
4	m-Cl-C_6H_4NH-	78	228(d)	$C_{15}H_{16}BrClN_2OS$	7.1	7.2	60	134(d)	$C_{15}H_{15}ClN_2OS$	9.3	9.1
5	p-Cl – C_6H_4NH-	75	235(d)	$C_{15}H_{16}BrClN_2OS$	7.4	7.2	60	175-76	$C_{15}H_{15}ClN_2OS$	9.3	9.1
6	p-Br – C_6H_4NH-	70	232(d)	$C_{15}H_{16}Br_2N_2OS$	6.7	6.5	69	210(d)	$C_{15}H_{15}BrN_2OS$	8.2	8.0
7	o-CH_3 – C_6H_4NH-	75	>250	$C_{16}H_{19}BrN_2OS$	7.9	7.6	75	144-45	$C_{16}H_{18}N_2OS$	10.0	9.8
8	m-CH_3 – C_6H_4NH-	77	>250	$C_{16}H_{19}BrN_2OS$	7.5	7.6	70	160-61	$C_{16}H_{18}N_2OS$	10.2	9.8
9	p-CH_3 – C_6H_4NH-	83	>250	$C_{16}H_{19}BrN_2OS$	7.7	7.6	65	180-81	$C_{16}H_{18}N_2OS$	9.8	9.8
10	o-OCH_3 – C_6H_4NH-	71	228(d)	$C_{16}H_{19}BrN_2O_2S$	7.1	7.3	67	191(d)	$C_{16}H_{18}N_2O_2S$	9.5	9.3
11	p-OCH_3 – C_6H_4NH-	75	251(d)	$C_{16}H_{19}BrN_2O_2S$	7.5	7.3	73	143-44	$C_{16}H_{18}N_2O_2S$	9.1	9.3
12	α-$C_{10}H_7NH-$	80	>250	$C_{19}H_{19}BrN_2OS$	7.2	7.0	63	195-96	$C_{19}H_{18}N_2OS$	8.9	8.7
13	β-$C_{10}H_7NH-$	78	>250	$C_{19}BrN_2OS$	7.2	7.0	66	192-93	$C_{19}H_{18}N_2OS$	8.6	8.7
14	p-NO_2 – C_6H_4NH-	68	>250	$C_{15}H_{16}BrN_3O_3S$	11.0	10.6	60	158-60	$C_{15}H_{15}N_3O_3S$	13.5	13.3
15	4-Cl – 2 – CH_3 – C_6H_3NH-	82	218(d)	$C_{16}H_{18}BrClN_2OS$	7.2	7.0	70	180(d)	$C_{16}H_{17}ClN_2OS$	9.0	8.8
16	2-Cl-4-CH_3 – C_6H_3NH-	70	>250	$C_{16}H_{18}BrClN_2OS$	6.6	7.0	75	166-67	$C_{16}H_{17}ClN_2OS$	8.9	8.7
17	2-Br-4-CH_3 – C_6H_3NH-	75	>250	$C_{16}H_{18}Br_2N_2OS$	6.5	6.3	68	174-75	$C_{16}H_{17}BrN_2OS$	7.9	7.7
18	4-Br-2-CH_3 – C_6H_3NH-	79	>250	$C_{16}H_{18}Br_2N_2OS$	6.0	6.3	69	210(d)	$C_{16}H_{17}BrN_2OS$	7.5	7.7
19	5-Cl-2,4-$(OCH_3)_2$ – C_6H_2NH-	74	224(d)	$C_{17}H_{20}BrClN_2O_3S$	6.5	6.3	73	206(d)	$C_{17}H_{19}ClN_2O_3S$	7.7	7.6
20	C_6H_5-	70	222(d)	$C_{15}H_{16}BrNOS$	4.4	4.1	70	160-62	$C_{15}H_{15}NOS$	5.8	5.5
21	CH_3-	65	260(d)	$C_{10}H_{14}BrMOS$	5.2	5.1	58	152-54	$C_{10}H_{13}NOS$	7.2	7.2
22	NH_2-	75	254(d)	$C_9H_{13}BrN_2OS$	10.3	10.1	70	205	$C_9H_{12}N_2OS$	14.2	14.3
23	NH_2NH-	--	—	—	—	—	64	231(d)	$C_9H_{13}N_3OS$	20.3	19.9
24	OH – *	--	—	—	—	—	62	238	$C_9H_{11}NO_2S$	7.0	7.1

* Prepared by heating a mixture of IV and potassium thiocyanate in hydrochloric acid.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1273-1274

Polyethyleneglycol Catalysed N-Sulphonylation & N-Benzoylation of Substituted Benzimidazoles

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Received 16 *April* 1986; *accepted* 19 *May* 1986

Benzenesulphonyl chloride and *p*-toluenesulphonyl chloride react with benzimidazole and 2-phenylbenzimidazole in benzene and 50% aqueous sodium hydroxide in the presence of polyethyleneglycol 400 or triethylbenzylammonium chloride to afford the corresponding N-sulphonyl derivatives. However, 2-methylbenzimidazole affords both N-sulphonylated and C-sulphonylated products. N-Benzoylation is also effected under similar conditions using benzoyl chloride.

A number of benzimidazole derivatives are known to possess various biological activities[1]. N-Sulphonylbenzimidazoles have been extensively used as pesticides and anthelmintics[2]. Imidazole on reaction with benzenesulphonyl chloride and *p*-toluenesulphonyl chloride gives the corresponding N-sulphonylated products[3]. However under similar conditions, reaction with benzimidazole fails to give N-sulphonylated products. Therefore, it was considered worthwhile to explore N-sulphonylation and N-benzoylation of substituted benzimidazoles (I, R = H, CH_3, Ph) catalysed by polyethyleneglycol (PEG 400) and phase transfer catalyst.

Benzimidazole and 2-methylbenzimidazole were synthesized by the condensation of formic acid and acetic acid with *o*-phenylenediamine[4]. 2-Phenylbenzimidazole was obtained by heating an intimate mixture of *o*-phenylenediamine and benzoic acid for 9 hr at 150° in the absence of PPA[5].

2-Methyl/phenyl-benzimidazoles when treated with sulphonyl chloride with stirring in a mixture of benzene and 50% aq. sodium hydroxide for 3-4 days led to the formation of traces of the sulphonylated product. However, in the presence of polyethyleneglycol (PEG 400) or triethylbenzyl ammonium chloride as a phase transfer catalyst, the above reaction could be completed in 30 min (Table 1); PEG 200 had almost negligible catalytic influence. Further, addition of excess of PEG complicated the reaction and only 3 to 4

Table 1 — N-Sulphonylated, N-Benzoylated and C-Sulphonylated Substituted Benzimidazoles (II & III)

Compound	R′	Reaction time (min) with		Recrystallisation solvent*	m.p. °C
		PEG 400	TEBA		
		N-Sulphonylation or benzoylation of I(R = H)			
II	$C_6H_5SO_2$	30	20	Petrol-ethyl acetate	95
IIA	*p*-$CH_3C_6H_4SO_2$	45	40	Petrol	98
IIB	C_6H_5CO	180	150	Ethyl acetate	118
		N-sulphonylation or benzoylation of I(R = CH_3)			
IIC	$C_6H_5SO_2$	50	35	25% Ethyl acetate -petrol*	109
IID	*p*-$CH_3C_6H_4SO_2$	70	60	35% Ethyl acetate -petrol*	112
IIE	C_6H_5CO	240	220	20% Benzene-petrol*	130
		N-Sulphonylation or benzoylation of I(R = C_6H_5)			
IIF	$C_6H_5SO_2$	300	250	$CHCl_3$-petrol	90
IIG	*p*-$CH_3C_6H_4SO_2$	500	480	Petrol-benzene	120
IIH	C_6H_5CO	800	800	Benzene	140
		C-Sulphonylation of I(R = CH_3)			
III	$C_6H_5SO_2$	50	35	45% Ethyl acetate-petrol*	Liquid
IIIA	*p*-$CH_3C_6H_4SO_2$	70	60	48% Ethyl acetate-petrol*	-do-
IIIB	C_6H_5CO	240	240	50% Benzene-petrol*	-do-

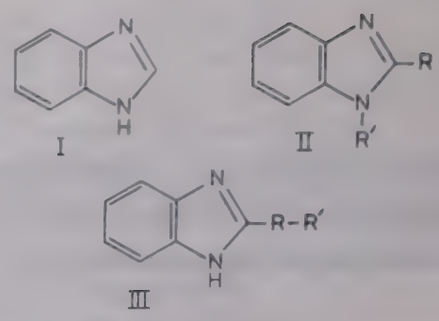
* Column Chromatographic separation over SiO_2

drops of PEG 400 were found necessary for a smooth reaction.

The reaction of sulphonyl chloride with 2-methylbenzimidazole (I, R = CH_3) afforded two products. The PMR spectrum of the less polar product exhibited a three-proton singlet at δ 2.75 in addition to the aromatic multiplet, whereas that of the more polar compound displayed a two-proton singlet at δ 5.11 and broad NH signal in the region δ 10.80-12.60, favouring the C-sulphonylated structure (III). The N-sulphonylated (II) and C-sulphonylated (III) products were obtained in the ratio 2.5:1.0 (PMR). Further the IR spectra of C-sulphonylated product displayed the νN – H at 3250-3370 cm^{-1} in addition to the sulphonyl group stretching at 1140 cm^{-1}. Treatment of N-sulphonylated derivative (II) with KOH/MeOH or sodium ethoxide afforded the desulphonylated product (I) in excellent yields.

The reaction of 2-methyl/phenyl-benzimidazoles (I, R = CH_3/Ph) with benzoyl chloride under similar condition afforded the substituted N-benzoylbenzimidazoles (II, R = CH_3/Ph; R′ = C_6H_5CO). The IR spectra of N-benzoylated benzimidazole displayed $\tilde{\nu}$C=O at 1720-1710 cm^{-1}. In the PMR spectra, the 7-H of N-benzoylbenzimidazoles (II) appeared at δ 6.77, which could be due to the shielding of the carbonyl group. The other aromatic protons appeared as a multiplet at δ 7.11-7.56. In general, the reaction with sulphonyl chlorides is faster in the presence of PEG 400 or triethylbenzylammonium chloride, while that with benzoyl chloride needs longer reaction period. IR or PMR data of the products (II and III) were consistent with the structures assigned.

Melting points were determined in open capillaries on a Toshniwal melting point apparatus and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer spectrophotometer and PMR spectra on a Jeol FX 90 MHz spectrophotometer using TMS as an internal standard (chemical shifts in δ ppm).



Sulphonylation/benzoylation: General procedure

To a stirred solution of benzimidazole (I, R = H, CH_3 or C_6H_5) (0.1 mol) in benzene (50 ml) and 50% aq. NaOH (50 ml) was added the sulphonyl chloride ($C_6H_5SO_2Cl$/*p*-CH_3. $C_6H_4SO_2Cl$/C_6H_5COCl) (0.12 mol) and 4 to 5 drops of PEG 400 or triethylbenzylammonium chloride (50 mg). Stirring was continued for the required time mentioned in Table 1. The organic layer on evaporation after washing with water and drying (Na_2SO_4) afforded the sulphonylated/benzoylated products (II or III) purified as mentioned in Table 1.

Desulphonation: General procedure

To a mixture of the N-sulphonylated benzimidazole (II, R = H, CH_3, C_6H_5) (0.1 mol) in CH_3OH (20 ml) was added with stirring KOH or C_2H_5ONa (0.1 mol) during 10 min. The reaction mixture was diluted with water (100 ml) and extracted with chloroform (2 × 20 ml). The chloroform layer on evaporation after drying (Na_2SO_4) afforded the substituted benzimidazole (I).

The author is thankful to Professor K Rajagopalan and P C Srinivasan for encouragement.

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1275-1276

A Facile Synthesis & Solvolysis of 4-[Bis(methylthio)]methylene-2-phenyl-2-oxazolin-5-one

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Received 24 *February* 1986; *accepted* 25 *March* 1986

2-Phenyl-2-oxazolin-5-one, generated in benzene by cyclising hippuric acid (**1**) with ethyl chloroformate in the presence of triethylamine, affords 4-[bis(methylthio)]methylene-2-phenyl-2-oxazolin-5-one (**2**), on reaction with carbon disulphide and subsequent methylation with methyl iodide in the presence of triethylamine. All these reactions occur in one-pot. Hydrolysis and alcoholysis of **2** give the acid (**3a**) and esters (**3b,c**), respectively.

In connection with our studies on 4-heteromethylene-2-oxazolin-5-ones[1], we required the title compound (**2**). The synthesis of **2** has been reported earlier[2] but the method is rather tedious. Also, its reactions do not seem to have been studied. In view of the importance of ketene dithioacetals[3,4], **2** appears to be potentially useful. In this note we present a facile one-pot syntheis of **2** and its rapid conversion into 2-benzoylamino-3-bis(methylthio)acrylic acid (**3a**) and its esters (**3b,c**).

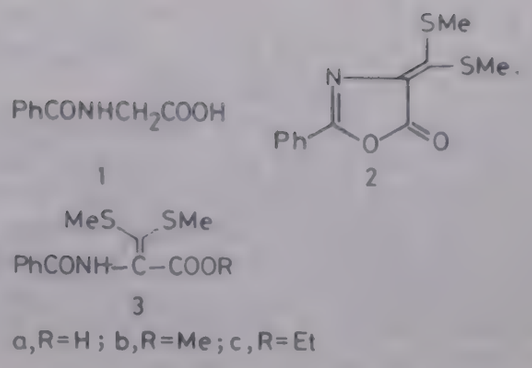
Cyclisation of hippuric acid with ethyl chloroformate and triethylamine in dry benzene, followed by triethylamine-mediated condensation with carbon disulphide and methylation by methyl iodide in the presence of Et_3N led to the formation of **2**. Work-up and purification by column chromatography afforded pure **2**.

Hydrolysis of **2** by ethanolic KOH for 30 min led to the acid (**3a**) along with a small amount of the ester (**3c**). Also, **2** gave **3b** and **3c** when heated in methanol and ethanol, respectively, using sodium alkoxide or KOH as a catalyst. It is noteworthy that the nucleophiles did not affect the ketene dithioacetal moiety. The same acid (**3a**) was also obtained by hydrolysis of the esters (**3**). Cyclisation of **3a** with ethyl chloroformate and triethylamine in dry benzene afforded **2** in excellent yield. The products synthesised were characterised by spectral data and elemental analyses.

All melting points are uncorrected.

4-[Bis(methylthio)]methylene-2-phenyl-2-oxazolin-5-one (**2**)

To a suspension of hippuric acid (3.58 g; 0.02 mol) in dry benzene (75 ml) containing triethylamine (3.9 ml; 0.028 mol), ethyl chloroformate (2.2 ml, 0.022 mol) was added and the mixture shaken at room temperature until the hippuric acid crystals completely dissolved and triethylamine hydrochloride separated. Triethylamine (5.6 ml; 0.04 mol) and carbon disulphide (3.6 ml; 0.06 mol) were added to the cooled mixture with constant stirring, followed by drop-wise addition of a solution of methyl iodide (3.8 ml; 0.06 mol) dissolved in benzene (10 ml). The mixture was stirred for additional 30 min in an ice-bath, solid salts obtained were filtered off, washed with benzene (3 × 5 ml) and the filtrate concentrated *in vacuo*. The residue was purified over silica gel column using benzene as an eluent, yield 1.27 g (24%, based on hippuric acid), m.p. 121-23° (lit.[2] m.p. 119-20°); PMR($CDCl_3$): 2.61 (*s*, 3H, S-CH_3), 2.85 (*s*, 3H, S-CH_3), 7.40-7.96 (*m*, 5H, Ar-H).



2-Benzoylamino-3-[bis(methylthio)]acrylic acid (**3a**)

A mixture of **2** (0.13 g, 0.0005 mol) and KOH (0.03 g, 0.0006 mol) and ethanol (10 ml) was refluxed for 30 min. The solvent was completely removed under reduced pressure, the residue treated with water (5 ml), filtered and washed with water. The filtrate was acidified with conc. HCl (1 ml) with cooling, the precipitate filtered, washed with water and re-crystallised from aq ethanol to afford the acid (**3a**), yield 0.10 g (71%), m.p. 143-45° (Found: C, 51.2; H, 4.7; N, 4.6. $C_{12}H_{13}NO_3S_2$ requires C, 50.9; H, 4.6; N, 4.9%); IR (nujol): 3250, 1700, 1650, 1610 PMR($CDCl_3$): δ 2.28 (*s*, 3H, S-CH_3), 2.34 (*s*, 3H, SCH_3); 2.62 (*b,s*, 1H, exchangable, COOH), 7.12-7.81 (*m*, 5H, Ar-H), 8.25 (*s*, 1H, exchangeable, CONH).

Ethyl 2-benzoylamino-3-[bis(methylthio)]acrylate (**3c**)

A mixture containing **2** (0.53, 0.002 mol), ethanol (30 ml) and KOH (0.02 g) was refluxed for 30 min. The solution was concentrated to dryness under reduced pressure, treated with water (10 ml) to give **3c** as a solid which was filtered, washed with water and

recrystallised from aq ethanol, yield 0.52 g (84%), m.p. 129-30° (Found: C, 54.3; H, 5.3; N, 5.6. $C_{14}H_{17}NO_3S_2$ requires C, 54.0; H, 5.5; N, 5.5%), IR (nujol): 3200, 1720, 1640; PMR ($CDCl_3$): δ 1.37 (*t*, 3H, CH_2-CH_3), 2.28 (*s*, 3H, S-CH_3), 2.34 (*s*, 3H, S-CH_3), 2.34 (*s*, 3H, SCH_3), 4.37 (*q*, 2H, CH_2CH_3), 7.12-7.84 (*m*, 5H, ArH), 8.34 (*b s*, 1H, exchangeable CONH).

Similarly was obtained the methyl ester (**3b**) when the reaction was carried out in methanol instead of ethanol; m.p. 120-21°; yield 84% (Found: C, 52.2; H, 5.3; N, 4.5. $C_{13}H_{15}NO_3S_2$ requires C, 52.5; H, 5.1; N, 4.7%); IR(nujol): 3200, 1720, 1640; PMR($CDCl_3$): δ 2.28 (*s*, 3H, S-CH_3), 2.34 (*s*, 3H, S-CH_3), 3.87 (*s*, 3H, OCH_3), 7.12-7.87 (*m*, 5H, Ar-H), 8.34 (*b s*, 1H, exchangeable, CONH).

Our thanks are due to the CSIR, New Delhi, for the award of a senior fellowship (to PKT) and a position in the Scientists' Pool (to JR).

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Indian Journal of Chemistry
Vol. 25B, December 1986, pp. 1277-1280

Synthesis of Some New 3-Methoxy-4-acylaminophenylisothiocyanates, 4′-Isothiocyanatophenoxyacetamides/ Isobutyramides as Possible Anthelmintic Agents†

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Received 22 *January* 1986; *accepted* 22 *May* 1986

A number of new 3-methoxy-4-acylaminophenylisothiocyanates (II and III), 4′-isothiocyanatophenoxyacetamides (IV) and 4-isothiocyanatophenoxyisobutyramides (V) have been synthesized and tested for anthelmintic, antiamoebic and antitrichomonal activities.

During our anthelmintic screening work on 6- and 7-isothiocyanatobenzoxazinones[1] (I), we observed marked antihookworm activity with 6-isothiocyanato-2, 2-dimethyl-1, 4-benzoxazin-3(4*H*)-one (I, $R_1 = R_2 = CH_3$, $-6-NCS$) in dogs and cats. In order to optimise this lead a series of 3-methoxy-4-acylaminophenylisothiocyanates (II and III), 4′-isothiocyanatophenoxyacetamides (IV) and isobutyramides (V) have now been prepared as open chain analogues of I and evaluated for their anthelmintic activity.

The starting N-acyl-4-nitro-*o*-anisidines (**2**) were prepared in good yields by the reaction of 4-nitro-*o*-anisidine (**1**) with different acid chlorides in acetone/K_2CO_3. Treatment of **1** with chloroacetyl chloride in AcOH/NaOAc gave **3** which on reaction with various secondary amines in acetone/K_2CO_3 gave the respective 4-nitro-N, N′-substituted-aminoacyl derivatives (**4**) in 80-85% yields.

4′-Nitrophenoxyacetamides (**11**) and isobutyramides (**12**) were prepared from the corresponding 4-nitrophenoxy acetates (**9**) and (**10**). Thus hydrolysis of **9** and **10** gave the acids which were converted into the acid chlorides by reaction with $SOCl_2$. Reaction of the acid chlorides, with various amines in $CHCl_3$, K_2CO_3 gave the required 4′-nitrophenoxyacetamides (**11a-j**) and isobutyramides (**12a-j**) in 75-80% yields.

Reduction of **2**, **4**, **11** and **12** with hydrazine hydrate-Raney nickel in boiling ethanol furnished the corresponding amino derivatives **5**, **6**, **13** and **14** in moderate yields. The IR spectra of **5**, **6**, **13** and **14** exhibited characteristic peaks around 3450 (NH_2) and 1670 cm^{-1} (amide C=O). The amino derivatives underwent smooth condensation with thiophosgene in aqueous acetone in the presence of $NaHCO_3$ to give the targetted isothiocyanato derivatives II (**7a-d & g**), III (**8a-d**), IV (**15a-i & l**) and V (**16a-i & l**) (Chart 1). The IR spectra of these compounds exhibited characteristic peaks for $-NCS$ (2100 cm^{-1}) carbonyl function (1670 cm^{-1}). The structures of the various isothiocyanates described in Table 1 were established on the basis of their correct elemental analyses and IR and PMR spectra of the representative compounds (see experimental).

Anthelmintic activity

All the compounds reported in Table 1 were tested for their anthelmintic activity against *Nematospiroides dubius* and *Hymenolepis nana* in mice and against *Nippostrongylus brasiliensis* and *Ancylostoma ceylanicum* in rats and hamsters respectively as described earlier[2]. Selected compounds were also tested for their antiamoebic activity *in vitro* against *Entamoeba histolytica* and antitrichomonal activity *in vitro* against *Trichomonas vaginalis* according to standard procedures[3].

Acylaminoisothiocyanates of type II (**7b & g**) and type III (**3a & d**) were found to possess a low order of activity (31-39%) against *N. dubius*. In addition compounds II (**7b**, **2 & g**) and III (**8b**) showed moderate antiamoebic activity *in vitro* against *E. histolytica* SLF-4 at 20, 50, 5 and 25 μg/ml concentrations respectively. None of the compounds showed any noteworthy activity against *H. nana*, *A. ceylanicum* and *N. brasiliensis*. They were also found to be inactive against *T. vaginalis*.

The anthelmintic screening results of various acylaminoisothiocyanates (II and III) as well as isothiocyanatophenoxyacetamides (IV) and isobutyramides (V) reported in this note indicate that the antihookworm activity exhibited by the parent isothiocyanatobenzoxazinones (I) was completely lost by cleaving any of the bonds in the oxazine ring system, although a few acylamino phenylisothiocyanates of types (II and III) showed some anthelmintic activity against *N. dubius* albeit of low order. None of the compounds exhibited any noteworthy antihookworm activity against *A. ceylanicum* in hamsters unlike the parent cyclic analogues.

†Communication No. 106 from IDPL Research Centre, Hyderabad 500 037.

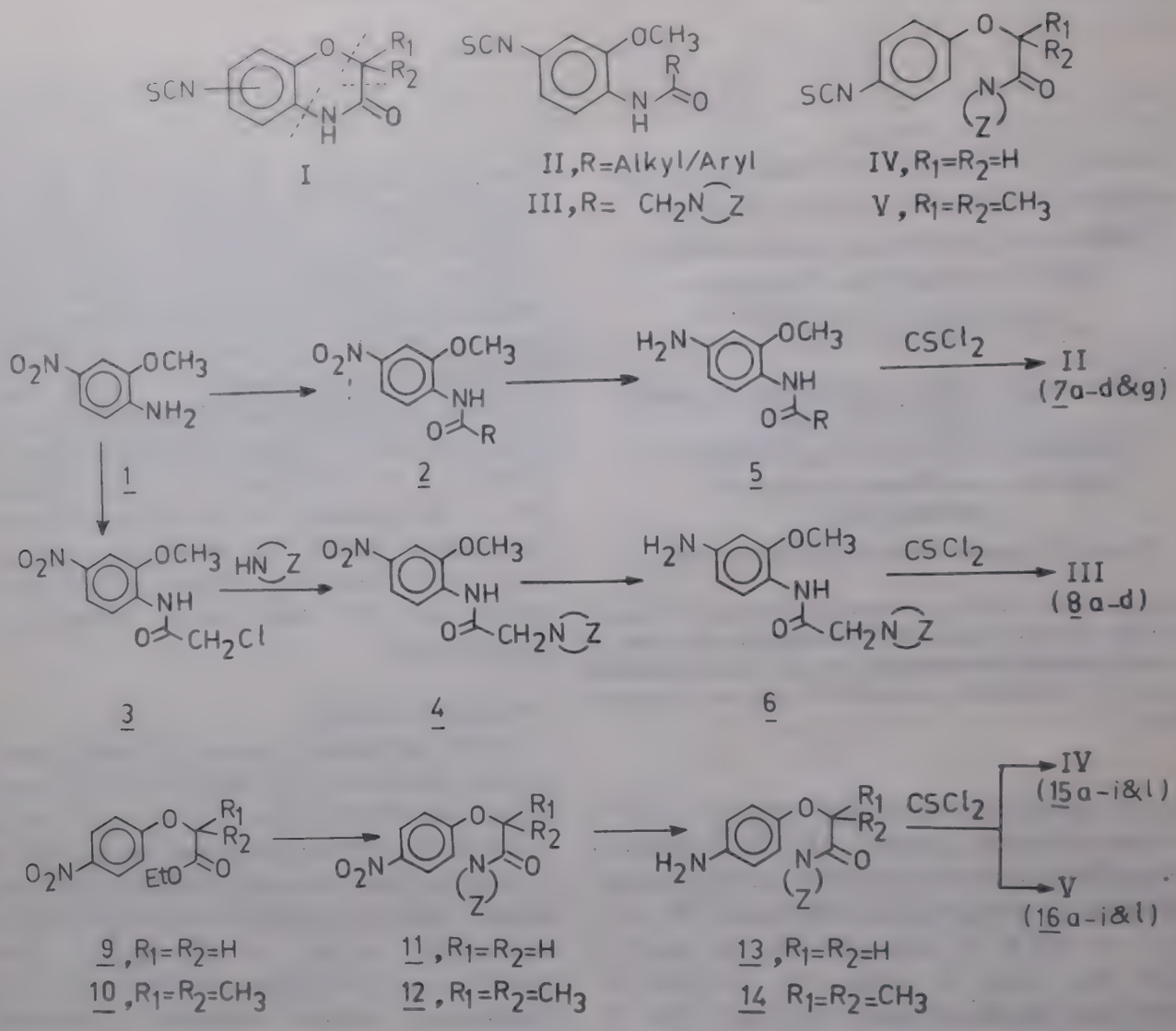

CHART 1

Melting points were determined in glass capillaries using Gallenkamp melting point apparatus and are uncorrected.

The methods described in the sequel are typical. Similar methods were followed for synthesising other compounds.

N-(2-Thenoyl)-4-nitro-o-anisidine (**2c**)

To a mixture of 4-nitro-*o*-anisidine (**1**) (16.8 g, 0.1 mol) and anhydrous K_2CO_3 (20 g) in acetone (100 ml) was added a solution of 2-thenoyl chloride (14.6 g, 0.1 mol) in acetone at 15°C. The mixture was refluxed for 1 hr, cooled, filtered and the filtrate evaporated *in vacuo* to give a yellow solid. It was filtered, washed with water, dried and recrystallized from ethanol to give pure **2c** (21.1 g, 76%) m.p. 155°. IR: 3380 (NH), 1720 cm^{-1} (C=O); PMR (acetone-d_6): δ 4.1 (*s*, 3H, OCH_3), 7.28 (*m*, 1H, thiophene H), 7.9 (*m*, 4H, ArH and thiophene H), 8.68 (*d*, 1H, ArC_6-H), (*d* 9.2 (*bs*, 1H, NH) (Found: C, 51.2; H, 4.0; N, 10.5. $C_{12}H_{10}N_2O_4S$ requires C, 51.8; H, 3.6; N, 10.1%).

The following compounds were similarly prepared (R, yield %, m.p.). **2a**, CH_2OCH_3, 67%, 109°; **2b**, 2-furyl, 73%, 180°; **2d**, $C_6H_4OCH_3$(*p*), 82%, 176°; **2e**, $C_6H_4NO_2$ (*p*), 85%, 214°.

N-Chloroacetyl-4-nitro-o-anisidine (**3**)

To a solution of **1** (16.8 g, 0.1 mol) in gl. acetic acid (100 ml) $ClCH_2COCl$ was added at 15°C, followed by a solution of sodium acetate (45 g) in water (200 ml). The mixture was shaken for 35 min, the product filtered, washed with 50% HCl, followed by water and dried. It was recrystallized from ethanol to give pure **3** (17.6 g, 72%), m.p. 112°; IR: 3320 (NH), 1690 cm^{-1} (C=O); PMR (acetone-d_6): δ 4.25 (*s*, 3H, OCH_3), 4.6 (*s*, 2H, $COCH_2$), 8.0 (*m*, 2H, ArH), 8.75 (*d*, 1H, ArC_6-H), 9.5 (*bs*, 1H, NH) (Found: C, 44.6; H, 4.1; N, 11.5. $C_9H_9ClN_4O_4$ requires C, 44.2; H, 3.7; N, 11.4%).

N-morpholinoacetyl-4-nitro-o-anisidine (**4b**)

To a mixture of **3** (24.4 g, 0.1 mol) and anhydrous K_2CO_3 (20 g) in acetone (100 ml) was added a solution

Table 1—Physical Data of Various New Isothiocyanates (II-V)

Compd*	Substituent	m.p. (°C)	Yield (%)	Mol. formula	N(%)†	
					Calc.	Found
		Compounds of type II				
7a	CH_2OCH_3	131	72	$C_{11}H_{12}N_2O_3S$	11.1	11.0
7b	2-Furyl	137	84	$C_{13}H_{10}N_2O_3S$	10.2	10.3
7c	2-Thienyl	128	79	$C_{13}H_{10}N_2O_2S_2$	9.7	10.0
7d	$C_6H_4OCH_3(p)$	131	65	$C_{16}H_{14}N_2O_3S$	8.9	9.1
7g	$C_6H_4NCS(p)$	184	62	$C_{16}H_{11}N_3O_2S$	12.3	12.6
		Compounds of type III (−NZ)				
8a	Piperidino	147	75	$C_{15}H_{19}N_3O_2S$	13.8	13.5
8b	Morpholino	142	67	$C_{14}H_{17}N_3O_3S$	13.6	13.2
8c	N^4-phenylpiperazino	127	82	$C_{20}H_{22}N_4O_2S$	14.6	14.3
8d	N^4-*m*-chlorophenyl-piperazino	125	63	$C_{20}H_{21}ClN_4O_2S$	13.4	13.1
		Compounds of type IV (−NZ)				
15a	Morpholino	103	73	$C_{13}H_{14}N_2O_3S$	10.0	9.3
15b	Pyrrolidino	102	82	$C_{13}H_{14}N_2O_2S$	10.7	10.9
15c	Piperidino	93	67	$C_{14}H_{16}N_2O_2S$	10.1	9.8
15d	N^4-methylpiperazino	101	56	$C_{14}H_{17}N_3O_2S$	14.4	14.0
15e	N^4-phenylpuperazino	108	76	$C_{19}H_{19}N_3O_2S$	11.9	12.1
15f	N-methyl	158	52	$C_{10}H_{10}N_2O_2S$	12.6	12.8
15g	N-hexyl(*n*)	67	63	$C_{15}H_{20}N_2O_2S$	9.6	10.0
15h	N-cyclohexyl 16	166	71	$C_{15}H_{18}N_2O_2S$	9.6	9.8
15i	N,N-diethyl	Oil	61	$C_{13}H_{16}N_2O_2S$	10.6	10.3
15l	$HN\text{-}C_6H_4\text{-}NCS(p)$	108	83	$C_{16}H_{11}N_3O_2S_2$	12.3	11.9
16a	Morpholino	198	67	$C_{15}H_{18}N_2O_3S$	9.1	8.9
16b	Pyrrolidino	201	86	$C_{15}H_{18}N_2O_2S$	9.6	9.6
16c	Piperidino	210	87	$C_{16}H_{20}N_2O_2S$	9.8	9.6
16d	N^4-methylpiperazino	Oil	53	$C_{16}H_{21}N_3O_2S$	13.1	12.9
16e	N^4-phenylpiperazino	Oil	66	$C_{21}H_{23}N_3O_2S$	11.0	11.2
16f	N-methyl	56	54	$C_{12}H_{14}N_2O_2S$	11.2	11.3
16g	N-hexyl(*n*)	67	67	$C_{17}H_{24}N_2O_2S$	8.7	8.3
16h	N-cyclohexyl	62	71	$C_{17}H_{21}N_2O_2S$	8.8	8.4
16i	$N(C_2H_5)_2$	52	83	$C_{15}H_{20}N_2O_2S$	9.6	9.7
16l	$HNC_6H_4NCS(p)$	175	67	$C_{18}H_{15}N_3O_2S_2$	11.4	11.7

*All the compounds were crystallized from benzene pet. ether.
†Satisfactory carbon and hydrogen analyses were obtained for all the compounds.

of morpholine (9.6 g, 0.11 mol) in acetone (20 ml) at 20°C, and the mixture was refluxed for 4 hr. It was filtered and the solvent removed from the filtrate *in vacuo*. The resulting solid was filtered, washed with water, dried and recrystallized from ethanol to give pure **4b** (24.5 g, 83%), m.p. 193°; IR: 3220 (NH), 1690 cm^{-1} (C=O); PMR (acetone-d_6): δ 2.9 (*m*, 4H, C_3- & C_5-protons of morpholine), 3.4 (*s*, 2H, $COCH_2$), 4.0 (*m*, 4H, C_2- & C_6-protons of morpholine); 4.41 (*s*, 3H, OCH_3), 8.15 (*m*, 2H, ArH), 8.9 (*d*, 1H, ArC_6-H) (Found: C, 52.7; H, 6.0; N, 14.1. $C_{13}H_{17}N_3O_5$ requires C, 52.9; H, 5.7; N, 14.2%).

The following compounds were similarly prepared (−NH) yield%, m.p.): **4a**, piperidino, 86%, 142°; **4c**, phenylpiperazino, 81%, 162°; **4d**, N^4-*m*-chlorophenyl-piperazino, 79%, 178°.

N-(4′-*Nitrophenoxyacetyl*)*morpholine* (**11a**)

This was prepared according to the method of Baker *et al.*[5] from 4-nitrophenoxyacetyl chloride. **11b**, **11c**, **11i** and the following compounds were similarly prepared (−NZ, yield, m.p.): **11d**, N^4-methyl-piperazino, 71%, 218°; **11e**, N^4-phenylpiperazino, 65%, 136°; **11f**, N-methyl, 73%, 158°; **11g**, N-*n*-hexyl(n), 82%, 51°; **11h**, N-cyclohexyl, 77%, 119°; **11j**, *p*-nitrophenyl, 86%, 138°.

N-(4′-*Nitrophenoxyisobutyryl*)*pyrrolidine* (**12b**)

To a mixture of 2-methyl-2-(4′-nitrophenoxy) propionoyl chloride[4] (2.43 g, 0.01 mol), $CHCl_3$ (25 ml) and K_2CO_3 (3.0 g) added a solution of pyrrolidine (0.8 g, 0.011 mol) in $CHCl_3$ (5 ml) at 10°C. The reaction mixture was refluxed for 4 hr, cooled, filtered and the

filtrate evaporated *in vacuo*. The resulting solid was filtered, washed with water, dried and recrystallized from ethanol to give pure **12b** (24.2 g, 87%), m.p. 68°; IR: 1640 (C=O); PMR ($CDCl_3$): δ 1.6 [*bs*, 10H, $C(CH_3)_2$ and 3, 4-methylene protons of pyrrolidine], 3.5 (*bs*, 4H, C_2- & C_5-protons of pyrrolidine ring), 6.85 (*d*, 2H, ArH), 8.1 (**d**, 2H, ArH) (Found: C, 60.8; H, 6.9; N, 10.4. $C_{14}H_{18}N_2O_4$ requires C, 60.4; H, 6.5; N, 10.1%).

The following compounds were similarly prepared (−NZ, yield %, m.p.): **12a**, morpholino, 82%, 110°; **12c**, piperidino, 19%, 95°; **12d**, N^4-methylpiperazinyl, 75%, 112°; **12c**, N^4-phenylpiperazinyl, 72%, 185°; **12f**, N-methyl, 74%, **12g**, hexyl(*n*), 80%, oil; **12h**, N-cyclohexyl, 77%, 136°; **12i**, NEt_2, 75% oil; **12j**, N-*p*-nitrophenyl, 85%, 165°.

N-(Acyl/Aroyl-4-amino-o-anisidines and 4'-aminophenoxyacetamides and isobutyramides (**5**, **6**, **13** *and* **14**): *General procedure*

To a solution of nitro compounds (**2**, **4**, **11** & **12**) (0.01 mol) and hydrazine hydrate (100%, 5 ml) in ethanol (100 ml) a catalytic amount of Raney nickel was added portionwise with stirring and the reaction mixture heated under reflux for 2 hr. It was filtered and the solvent removed *in vacuo*; the residual solid was filtered, washed with water, dried and recrystallized from ethanol. Some of the amino compounds obtained as oils were used as such in the next reaction. The yields and melting points of the various amino compounds are as follows. (R, yield %, m.p.): **5a**, CH_2OCH_3, 76%, 57°; **5b**, 2-furyl, 82%, 113°, **5c**, 2-thienyl, 63%, oil; **5d**, $C_6H_4OCH_3(p)$, 78%, 136°; **5f**, $C_6H_4NH_2(p)$ 86%, 135°. (−NZ, yield, m.p.): **6a**, piperidino, 67%, oil; **6b**, morpholino, 62%, **6c**, N^4-phenylpiperazino, 73%, 150°; **6d** N^4-*m*-chlorophenylpiperazino, 69%, 121°.

4'-Aminophenoxyacetamides and isobutyramides (−NZ, yield %, m.p.): **13a**, morpholino, 62%, 138°; **13b**, pyrrolidino, 81%, 130°; **13c**, piperidino, 79%, oil; **13d**, N^4-methylpiperazino, 68%, 73°; **13e**, N^4-phenylpiperazino, 73%, 82°; **13f**, N-methyl, 67%, 108°; **13g**, N-*n*-hexyl(*n*), 76%, 78°; **13h**, N-cyclohexyl, 78%, 87°; **13i**, $N\text{-}Et_2$, 82% oil; **13k**, $N\text{-}C_6H_4NH_2(P)$, 77%, 102°; **14a**, morpholino, 86%, 92°; **14b**, pyrrolidino, 82%, 118°; **14c**, piperidino, 83%, 80°; **14d**, N^4-*p*-methylpiperazino, 76%, 182°; **14e**, N^4-phenylpiperazino, 78%, 98°; **14f**, N-methyl, 61%, oil; **14g**, N-hexyl(*n*), 56%, oil; **14h**, N-cyclohexyl, 63%, 81°; **14i**, NEt_2, 78%, oil; **14k**, $N\text{-}C_6H_4NH_2$, 84%, 88°.

3-*Methoxy*-4-(4'-*isothiocyanatophenyl carbonyl*) *aminophenyl isothiocyanate* (7 *g*)

To a stirred mixture of **5f** (2.57 g, 0.01 mol) and $NaHCO_3$ (3.36 g, 0.04 mol) in acetone (50 ml) and water (5 ml) was added dropwise a solution of thiophosgene (2.3 g, 0.02 mol) in acetone (5 ml) at room temperature. The reaction mixture was stirred for 1 hr, diluted with water (50 ml) and the resulting solid filtered, washed with water, dried and recrystallized from benzene to give pure **7g** (2.1 g, 62%), m.p. 184°; IR (nujol): 3420 (NH), 2130 (NCS), 1670 cm^{-1} (C=O); PMR ($CDCl_3$): δ 4.05 (*s*, 3H, OCH_3), 7.1-8.35 (*m*, 7H, ArH), 9.8 (*s*, 1H, NH) (Found: C, 56.5; H, 3.4; N, 12.6. $C_{16}H_{11}N_3O_2S_2$ requires C, 56.3; H, 3.2; N, 12.3%).

Compounds **7a-d**, **8a-d**, **15a-i** & **l**, and **16a-i** & **l** listed in Table 1 were similarly prepared.

The authors thank Dr C D Lovekar and staff for anthelmintic screening. They also thank the analytical staff of this Centre for spectral and elemental analyses.

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Regd No. D(C)-1018